(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28847 A1

(51) International Patent Classification[7]: C07D 285/135, 271/113, 417/04, 417/10, 417/12, 417/14, 453/02, A61K 31/433, 31/55, 31/439, 31/4245, 31/4439, 31/4709, 31/497, A61P 29/00, 37/00

(21) International Application Number: PCT/EP01/11330

(22) International Filing Date: 1 October 2001 (01.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00402710.8 2 October 2000 (02.10.2000) EP

(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): VERGNE, Fabrice [FR/FR]; 1, allée du champ de la mare, F-91190 Gif sur Yvette (FR). DUCROT, Pierre [FR/FR]; 6 résidence d'Amblainvilliers, F-91370 Verrieres le Buisson (FR). ANDRIANJARA, Charles [FR/FR]; 3 rue Auguste Daix, F-94260 Fresnes (FR). BERNARDELLI, Patrick [FR/FR]; 146 rue Boucicaut, F-92260 Fontenay aux Roses (FR). LORTHIOIS, Edwige [FR/FR]; 6 rue de la Briquetterie, F-75014 Paris (FR).

(74) Agent: HIRSCH, Denise; Warner-Lambert Company, c/o Parke-Davis, Pfizer Global Research & Development, Fresnes Laboratories, 3-9 rue de la Loge, F-94265 Fresnes (FR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

(57) Abstract: The invention provides 1,3,4-thiadiazoles and 1,3,4-oxadiazoles having the following formula (I):in which, Y is S or O,R1 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl or a polycyclic group, optionally substituted,R2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl or aryl optionally substituted,R3 is X_2-R'3, in which X_2 is a binding group and R'3 is cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl, or a polycyclic group; optionally substituted,or their pharmaceutically acceptable derivatives,the process for their preparation and their use for the manufacture of a medicament for the treatment of disorders for which a treatment by a PDE7 inhibitor is relevant.

WO 02/28847 A1

NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

Field of the invention.

The invention relates to novel thiadiazoles and oxadiazoles, processes for their preparation, and their use as phosphodiesterase 7 (PDE7) inhibitors.

Background of the invention.

Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, substrate specificity or sensitivity to cofactors or inhibitory drugs.

Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterisation showed a high-affinity cAMP-specific PDE (Km=0.2 μM), that was not affected by cGMP potent selective PDE isoenzyme inhibitors.

PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway epithelial (AE) cell lines and several foetal tissues.

Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be devoid

of the side effects associated with known selective inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

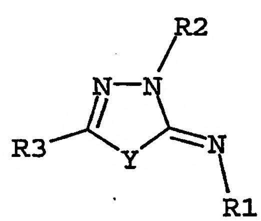
A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations, i.e. micromolar inhibibitor, preferably nanomolar inhibitors.

Summary of the invention.

The invention provides pharmaceutical compositions comprising a compound having the following formula (I):



(I)

wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4,

identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:
  1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
  2) $COOR_5$, OR_5, SO_2R_5,
  3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:

- X_2 is a single bond or,
  a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
  1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
  2) OR_5, $=NR_5$ or,
  3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:
cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
    - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, $X_5-N(R_{19})-R_{18}$ in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
    - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21},or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;
- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or $X_5-N(R_{19})-R_{18}$ in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

The invention also relates to novel compounds having the following formula (I) above.

These compounds are selective PDE7 inhibitors. They can be used in the treatment of various diseases, such as T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, central nervous system (CNS) diseases, allergic diseases, endocrine or exocrine pancreas diseases, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

The invention also relates to a process for preparing the above compounds.

The invention further concerns the use of a compound of formula (I) for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

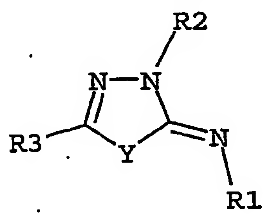
The invention also provides a method for the treatment of a disorder for which therapy by a PDE7 inhibitor is relevant, comprising administering to a mammal in need thereof an effective amount of compound of formula (I).

The invention also concerns a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the treatment of a disorder for which therapy by a PDE7 inhibitor is relevant, comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

Detailed description of the invention.

The present invention provides pharmaceutical compositions comprising compounds having formula I,



(I)

in which R1, R2, R3 and Y are as defined above with the exclusion of the compounds recited above.

In the following and in the foregoing text:

- aryl is understood to refer to an unsaturated carbocycle, exclusively comprising carbon atoms in the cyclic structure, the number of which is between 5 and 10, including phenyl, naphthyl or tetrahydronaphthyl;

- heterocycle is understood to refer to a non-saturated or saturated monocycle containing between 1 and 7 carbon atoms in the cyclic structure and at least one heteroatom in the cyclic structure, such as nitrogen, oxygen, or sulfur, preferably from 1 to 4 heteroatoms, identical or different, selected from nitrogen, sulfur and oxygen atoms. Suitable heterocycles include morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, pyrimidinyl, 2- and 3-furanyl, 2- and 3-thienyl, 2-pyridyl, 2- and 3-pyranyl, hydroxypyridyl, pyrazolyl, isoxazolyl, tetrazole, imidazole, triazole and the like;

- polycyclic groups include at least two cycles, identical or different, selected from aryl, heterocycle, cycloalkyl, cycloalkenyl groups fused together to form said polycyclic group such as 2- and 3-benzothienyl, 2- and 3-benzofuranyl, 2-indolyl, 2- and 3-quinolinyl, acridinyl, quinazolinyl, indolyl benzo[1,3]dioxolyl and 9-thioxantanyl;

Preferred polycyclic groups include 2 or 3 cycles as defined above.

More preferred polycyclic groups include 2 cycles (bicyclic substituents) as defined above.

- bicyclic groups refer to two cycles, which are the same or different and which are chosen from aryl, heterocycle, cycloalkyl or cycloalkenyl, fused together to form said bicyclic groups;

- halogen is understood to refer to fluorine, chlorine, bromine or iodine;

- lower alkyl is understood to mean that the alkyl is linear or branched and contains 1 to 6 carbon atoms; Examples of lower alkyl groups include methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl, n-butyl, pentyl, hexyl and the like.

- alkenyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several double bonds, preferably one or two double bonds. Preferred alkenyls comprise from 3 to 6 carbon atoms and one double bonds.

- alkynyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several triple bonds, preferably one or two triple bonds. Preferred alkynyls comprise from 3 to 6 carbon atoms and one triple bonds.

- lower haloalkyl are understood to refer to a lower alkyl substituted with one or several halogens; Preferred lower haloalkyl groups include perhaloalkyl groups such as CF_3.

- cycloalkyl is understood to refer to saturated monocarbocyle containing from 3 to 10 carbon atoms; preferred cycloalkyl groups comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

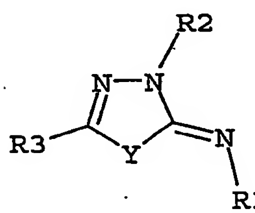
- cycloalkenyl is understood to refer to unsaturated monocarbocyle containing from 3 to 10 carbon atoms. Preferred cyloalkenyl groups contain 1 or 2 double bonds. Examples of suitable cycloalkenyl are 3-cyclohexene, 3-cycloheptene or the like.

- carboxylic acid bioisostere has the classical meaning; common carboxylic acid bioisostere are tetrazol, hydroxamic acid, isoxazole, hydroxythiadiazole, sulfonamide, sulfonylcarboxamide, phosphonates, phosphonamides,

phosphinates, sulfonates, acyl sulfonamide, mercaptoazole, acyl cyanamides.

Preferred pharmaceutical composition are those containing a compound of formula (I) in which R1, R2, R3 and Y are as defined above, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH_2)_3$-C(=O)OCH_2CH_3.

The present invention also relates to compounds of formula (I),


(I)

in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, C(=O)R_5, C(=S)R_5, SO_2R_5, SOR_5, SO_3R_5, SR_5,

OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  - lower alkyl,
  - C_2-C_{10} alkenyl,
  - C_4-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or, a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

    2) OR_5, $=NR_5$ or,

    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or

different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;
  4) heterocycle optionally substituted with one or several groups R_5;

wherein, R_5, R_6, R_9 and R_{10} are as defined above,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,
- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,

1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,

1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,

Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,

2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,

2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,

2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,

2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

Preferred compounds of formula (I) are those in which R1, R2, R3 and Y are as defined above, with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

Other preferred compounds of formula (I) are those in which

- R1 is:
  - C_4-C_6 alkyl,
  - cycloalkyl,
  - cycloalkenyl,

heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$.

Other preferred compounds of formula (I) are those in which R2 is lower alkyl.

Further preferred compounds of formula (I) are those in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$,

$C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

Particularly preferred compounds of formula (I) are those in which R1 is:

cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.

Other particularly preferred compounds of formula (I) are those in which R2 is CH_3.

Further particularly preferred compounds of formula (I) are those in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

More preferred compounds of formula (I) are those in which
- R1 is:
  C_4-C_6 alkyl
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl,
  or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:
- X_1 is a single bond a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,

R2 is lower alkyl, and,

R3 is X_2-R'$_3$ wherein,
- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene and,

- R'3 is:
  cycloalkyl,
  cycloalkenyl,
  aryl,
  heterocycle,
  or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

Other more preferred compounds of formula (I) are those in which,

R1 is:
  cycloalkyl, preferably cyclohexane,
  cycloalkenyl,
  aryl, preferably phenyl,
  or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$,

R2 is CH_3, and,

R3 is X_2-R'3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

Other more preferred compounds of formula (I) are those in which,

Y is O,

R1 is:

cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,

- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$,

R2 is CH_3, and,

R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

  cycloalkyl,
  aryl, preferably phenyl
  heterocycle,
  or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

More specifically, a group of compounds of formula (I) which has been found to be of particular interest are those in which,

R1 is:

  cyclohexane,
  phenyl
  or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3,
  2) COOH, OH,
  3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

Most preferred compounds of formula (I) are those in which Y is S.

Preferably, in each of the above definition of R1:

- R_5 is selected from
  - H, or,
  - lower alkyl, optionally substituted with OH, preferably CH_3.
- R_6 is selected from

- H, or,
- lower alkyl,preferably CH_3.
- R_9 and R_{10} are selected from
  - H, or,
  - lower alkyl, preferably CH_3.

Preferably, in each of the above definition of R2:
- R_5 and R_6 are selected from
  - H, or,
  - lower alkyl, preferably CH_3.
- R_9 and R_{10} are selected from:
  - H, or,
  - lower alkyl, preferably CH_3.

Preferred compounds are:

I1	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I1.1	(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I1.2	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
I1.7	2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
I1.9	{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol
I1,10	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I2.1	5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
I2.2	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid
I3	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine
I3.1	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol

I3.3	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine
I3.4	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
I3.7	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
I3.8	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine
I3.10	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol
I3.11	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
I3.13	tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.14	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine
I3.15	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I3.16	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine
I3.17	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I3.18	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
I3.19	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine
I3.20	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
I3.25	(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I3.26	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine
I4	3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I5	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol

I6	5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
I6.1	(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.3	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I6.5	(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I6.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine
I6.8	(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.9	{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
I6.11	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide
I7	Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I8	(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I8.1	5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
I8.2	3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
I8.3	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid
I8.4	(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine
I9	(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I10	Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I10.1	[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I11	Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I12	Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I13	[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I14	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
I15	Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I15.1	[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
I15.2	Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine-
I16	2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
I17	Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I17.1	Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I17.2	Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I18	[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I18.1	Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I18.2	Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I18.3	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid
I18.4	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid
I18.5	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I18.6 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I19 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I19.1 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide

I19.2 {5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine

I19.3 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide

I19.4 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.5 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide

I19.6 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.7 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.8 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide.

I19.9 C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide

I19.10 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide

I19.11 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide

I19.12	2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide
I19.14	2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide
I20	[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester
I21	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
I21.1	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid
I21.2	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I21.3	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide
I21.4	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
I22	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol
I23	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol
I23.1	6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
I23.2	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol
I24	2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol
I25	Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I26	5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol
I27	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol
I28	Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I29 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine

I30 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I31 [5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid

I31.1 2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I32 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I33 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I34 Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I35 [5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I35.1 Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I35.2 Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I36 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol

I37 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I37.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

I37.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide

I37.3 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.4 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

I37.5	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide
I37.6	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide
I37.7	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide
I37.8	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide
I37.8-1	Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine
I37.9	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide
I37.10	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide
I37.11	2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide
I37.12	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide
I37.13	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
I37.13-1	4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide
I37.14	[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone
I37.15	2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
I37.15-a	(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,

I37.16 (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,

I37.16-a (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid

I37.17 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone

I37.18 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone

I37.19 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide

I37.20 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,

I37.21 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone

I37.22 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide

I37.23 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

I37.24 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide

I37.25 N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.26 N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.27 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide

I37.28	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide
I37.28-1	[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I37.29	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
I38	Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I39	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
I40	(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine
I41	Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I42	4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
I43	4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
I44	4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I45	4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I46	5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
I47-a	4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I47-b	4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I48	4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I49	4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I50	4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I51	4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I52-a	4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I52-b	4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I53	(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I54	4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid
I55	4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide
I56	4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid
I57	4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide
I58	4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide
I59	N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I60	N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I61	N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

I62	1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester
I63	4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I64	4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I65	4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I66	4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I67	5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
I68	4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I69	4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I70	4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I71	4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I72	4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I73	4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I74	4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I74.1	4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I75	4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I76	4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I77	4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

I78 (1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol

I79 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid

I80 3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I80.1 3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I81 2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I82 3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid

I83 [5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine

I84 [5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine

I85 3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I86 N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

I87 N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

I88 N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

I89 *N*-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide

I90 3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile

I90.1 [5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine

I90.2 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine

I90.3 3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol

I91 [5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I91.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile

I91.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide

I92 [5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

I92.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide

I92.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide

I93 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester

I93.1 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I93.2 2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I93.3 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I93.4 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one

I93.5 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine

I93.6 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione

I94 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

I95 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

I96 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

I96.1 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I97.1 3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I98 3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I99 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

I99.1 Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine

I100 Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I100.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine

I100.2 [5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.3 N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide

I100.4 [5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

I100.5 [5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)- phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.6 (E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine

I100.7 [5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.8 [5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.9 Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide

I100.10 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea

I100.11 1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea

I101 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I102 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I102.1 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I103 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I104 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester

I104.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide

The compounds utilised in the invention include pharmaceutically acceptable derivatives of compounds of formula (I) such as solvates, hydrates, pharmaceutically acceptable salts and polymorphs (different crystalline lattice descriptors).

Pharmaceutically acceptable salts of a compound of formula (I) include salts having a basic part and salts having an acidic part.

The expression pharmaceutically acceptable salt of a compound of formula (I) having a basic part should be understood to refer to the addition salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic acids such as, for example, hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulfonic and isethionic acid salts, and the like. The various quaternary ammonium salts of the derivatives (I) are also included in this category of compounds of the invention. In addition, the expression pharmaceutically acceptable salt of a compound of formula (I) having an acidic part is

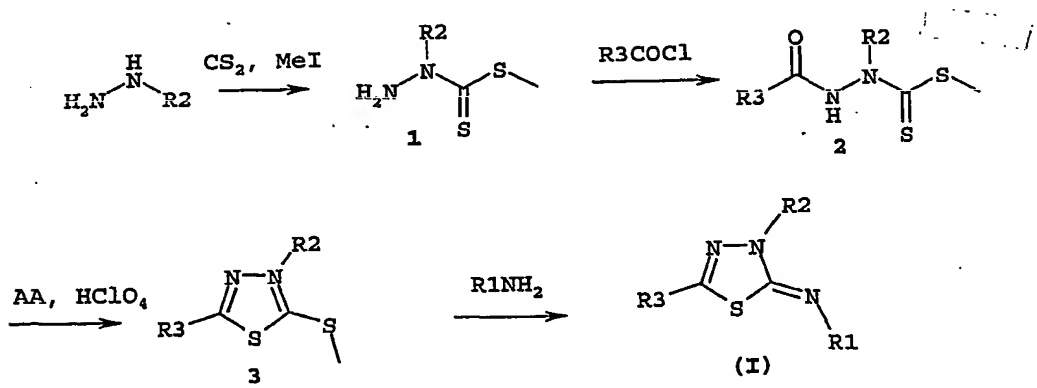
understood to refer to the usual salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic bases such as, for example, the hydroxides of alkali metals and alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide. (See also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, which is incorporated herein by reference.).

Use of a prodrug of a compound of the invention such as would occur to one skilled in the art (see Bundgaard, *et al.*, Acta Pharm. Suec., 1987; **24**: 233-246), is also contemplated.

Process for the preparation.

The compounds of this invention can be synthesised according to the general procedures of synthesis A-E, utilising methodology described herein which is known to a person skilled in the art.

Protocol A:



The starting compounds are either commercially available or can be prepared according to routes known to

the skilled man. See M. Akbar Ali, S.E. Livingston, and D.J. Philipps, *Inorganica Chimica Acta*, 6, 11 (1972); P. Molina, A. Tarraga, A. Espinosa; *Synthesis*, 690 (1988); P. Molina, A. Tarraga, A. Espinosa; *Heterocycles*, vol.29, N°12 (1989).

In step 1, the substituted hydrazine is reacted with carbon disulphide and with an alkyl-iodide such as methyl-iodide to form the desired 2-substituted S-alkyldithiocarbazate (1). Various solvents, operating conditions, bases, can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction of the substituted hydrazine with carbon disulphide an alcoholic solution of potassium hydroxide with a temperature not exceeding 15°C. Methyl iodide can be added to this solution or to a diluted solution (e.g. with water).

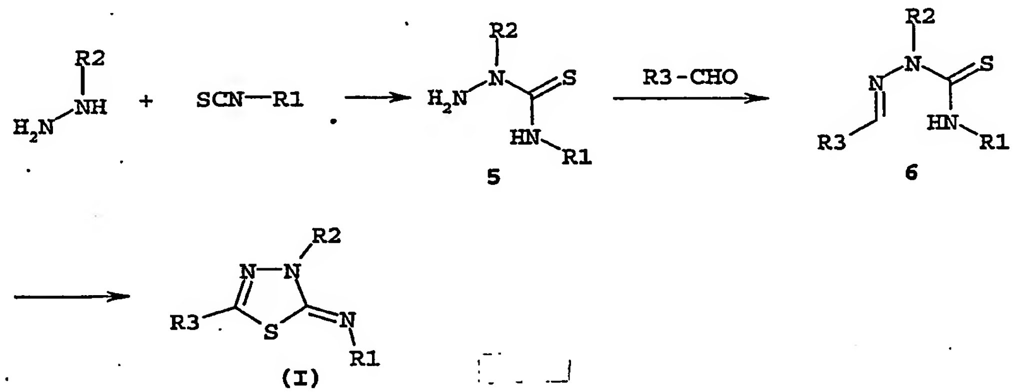
In step 2, the substituted S-methyldithiocarbazate is reacted with an appropriate group R3CO-X in which X is a leaving group such as halogen. Preferably, R3CO-X is an acyl chloride (R3COCl). The reaction can be carried out in e.g. toluene as the solvent at reflux. The corresponding acylated methyldithiocarbazate (2) is obtained.

In step 3, the acylated methyldithiocarbazate is cyclized into the desired 1,3,4-thiadiazole. The reaction can be carried out in the presence of acetic anhydride (AA) and perchlorate $HClO_4$ in ether, preferably, at a temperature comprised between -5 and 5°C, preferably 0°C, or in the presence of trimethylsilyl trifluoromethanesulfonate in dichloromethane, preferably, at a temperature comprised between 0 and 25°C. After stirring at room temperature several hours, an intermediate compound which is the 1,3,4-thiadiazolium perchlorate (3) is obtained.

In step 4, the 1,3,4-thiadiazole (or its perchlorate or sulfonate) is reacted with a suitable amine $R1NH_2$, to form the final compound. The reaction can be carried out in alcool such as ethanol as a solvent (the solvent may also be an aprotic solvant such as dioxane, dimethylformamide (DMF) or acetonitrile), in the presence of a base such as

triethylamine, and preferably, at a temperature comprised between 40 and 110°C, preferably between 40 and 80°C.

Protocol B :



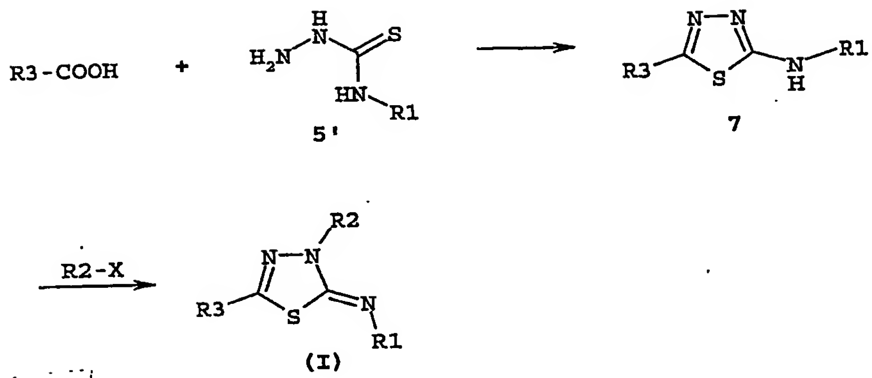
The starting compounds are either commercially available or can be prepared according to routes known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; *J. Heterocyclic Chem.*, 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcool e.g. methanol and/or water at a temperature comprised between -5°C and 15°C, preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with an aldehyde R3CHO to form the desired thiosemicarbazone (6). The reaction can be carried out in alcool e.g. methanol, at a temperature comprised between 50 and 90°C, preferably 75°C.

In step 3, the substituted thiosemicarbazone is cyclized to yield compound (I). The reaction can be carried out in alcool, e.g. ethanol, at a temperature comprised between 20°C and 110°C, preferably 75°C, in the presence of an oxidant such as $FeCl_3$.

Protocol C :

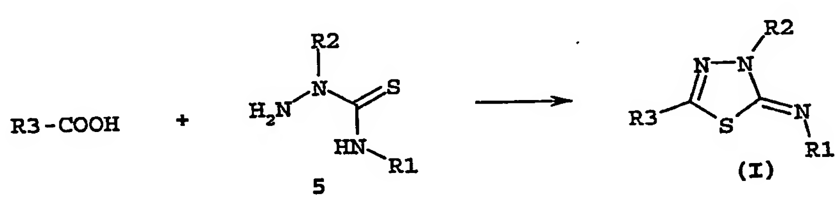


The starting compounds are either commercially available or can be prepared according to routes known to the skilled man. See FR-A-7712352, DE-A-4418066 and FR-A-8015072.

In the first step, the carboxylic acid is reacted with the thiosemicarbazide derivative (5') to yield the desired 1,3,4-thiadiazole (7). The reaction can be carried out in an aprotic solvant such as dioxane, at reflux, in the presence of a deshydrating agent, eg $POCl_3$.

In the second step, the desired 1,3,4-thiadiazole is reacted with R2X, where X is a leaving group such as trifluoromethane sulfonate, iodide or bromide. The reaction can be carried out in an aprotic solvent such as dioxane or DMF (if R2-X is alkyl-iodide or bromide), preferably at room temperature (RT) or under heating to yield compound (I).

Protocol D : 1 step



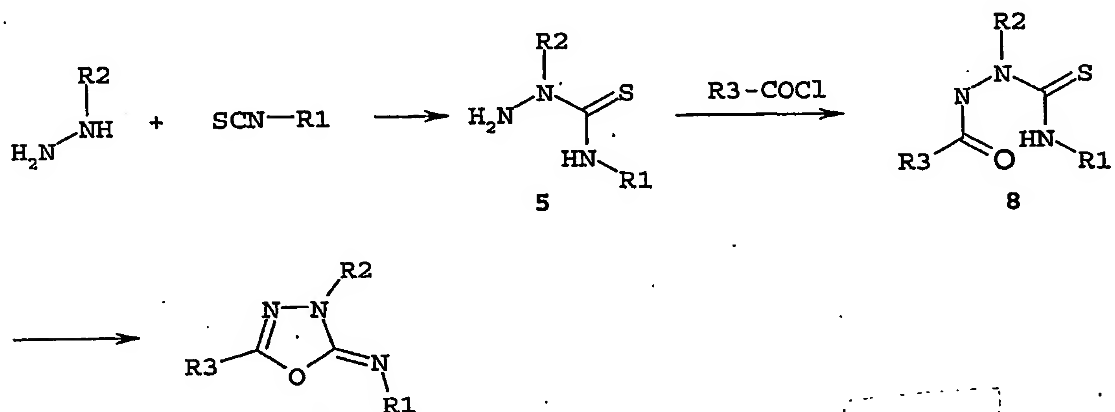
The starting compounds are either commercially available or can be prepared according to routes known to the skilled man.

In the first step, the carboxylic acid is reacted with the substituted thiosemicarbazide derivative (5) to yield

the desired final 1,3,4-thiadiazole (I). The reaction can be carried out in an aprotic solvent such as dioxane, at reflux and at a temperature comprised between 75 and 120°C, in the presence of a deshydrating agent, e.g $POCl_3$.

The solvent, reaction time, temperature, catalyst if any, can be varied in all steps described above for all routes, as the skilled man will appreciate.

Protocol E : 3 step



See J.M. Kane, M.A. Staeger, Synthetic communication, 22 (1), 1-11 (1992).

The starting compounds are either commercially available or can be prepared according to methods known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; J. Heterocyclic Chem., 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcool e.g. methanol and/or water at a temperature comprised between -5 and 15°C preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with the acid chloride to form the desired thiosemicarbazide (8). The reaction can be carried out in a basic medium such as pyridine at room temperature, or in an aprotic solvent in the presence of a base such as pyridine or triethylamine.

In step 3, the substituted thiosemicarbazide is

cyclized to yield compound (I). The reaction can be carried out in alcool, e.g. methanol, at a temperature of e.g. 75°C, in the presence of Mercuric oxide (HgO).

Pharmaceutical compositions.

The products of the invention are administered in the form of compositions, which are appropriate depending on the nature, and severity of the condition to be treated. The daily dose in humans is usually between 2 mg and 1 g of the active ingredient, which may be taken in one or more individual doses. The compositions are prepared in forms which are compatible with the intended route of administration, such as, for example, tablets, coated tablets, capsules, mouthwashes, aerosols, powders for inhalation, suppositories, enemas, foams (such as rectal foams) gels or suspensions. These compositions are prepared by methods which are familiar to those skilled in the art and comprise from 0.5 to 60% by weight of active ingredient (compound of the invention) and 40 to 99.5% by weight of a pharmaceutical vehicle or carrier which is appropriate and compatible with the active principle and the physical form of the intended composition.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders, tablets, cachets or encapsulated forms for capsules preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl

cellulose, a low-melting wax, cocoa butter, and the like.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration. The drug may be delivered as a spray (either in a pressurised container fitted with an appropriate valve or in a non-pressurised container fitted with a metering valve).

Liquid form preparations include solutions, suspensions, and emulsions.

Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify. Enemas are obtained according to known procedures to prepare solutions adapted for rectal administration. Foams are prepared according to known methods (these foams can notably be similar to those used to administer a drug such as 5-ASA for treating rectocolite).

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of drug. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for

example, packaged tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Methods of treatment.

The compounds of the invention are selective PDE7 inhibitors. They can be used in the treatment of various diseases, as they can modulate inflammatory and immunological processes due to an increase of intracellular cAMP levels.

The diseases that can be successfully treated include namely T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

The compounds of the invention have low IC50 values, typically at most 5 μM, preferably below 1 μM, and even below 100 nM.

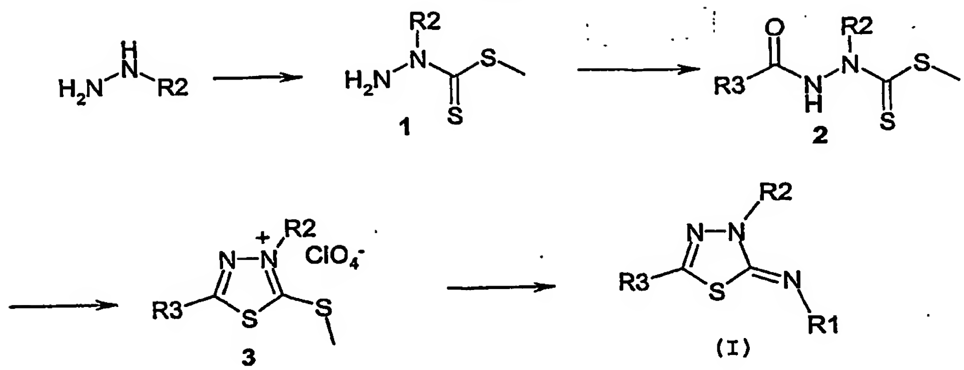
The invention finally relates to a method for the treatment of the above-mentioned diseases comprising administering to a mammal, particularly a human, in need thereof an effective amount of compound of the invention.

The following examples illustrate the invention without limiting it.

Examples

Compounds of the invention have been named with the software "AutoNom Version 4.0"

Protocol A :



Intermediate 1 : PROTOCOL A

Intermediate 1a: R2= methyl
***N*-Methyl-hydrazinecarbodithioic acid methyl ester**

Methylhydrazine (370 mmol, 19.43 mml) was added to a solution of potassium hydroxide (370 mmol, 20.7 g) in 90% aqueous alcohol (130 mL). The mixture was cooled to 5°C, then carbon disulphide (370 mmol, 22.2 ml) was added dropwise with vigorous stirring, over 1h, while the temperature of the mixture was not allowed to rise above 7°C. The resulting yellow solution was diluted with water (300 ml) and the methyl iodide (370 mmol, 23.34 ml) was added slowly while the mixture was stirred vigorously. After the stirring had been continued for 3 h at 10-15°C, the white crystals of 2-methyl-S-methyldithiocarbazate (**1a**) were filtered off, washed with a mixture 1:1 of ethanol:petroleum ether to give 38 g of the desired compound.

Yield: 84%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.32 (s, 3H), 3.60 (s, 3H), 5.55 (s, 2H).

Intermediate 2: PROTOCOL A

Intermediate 2a: R2= methyl, R3= 4-chloro-phenyl
***N'*-[1-(4-Chloro-phenyl)-methanoyl]-*N*-methyl-hydrazinecarbodithioic acid methyl ester**

The appropriate acyl chloride (73.39 mmol, 9.30 ml) (R3COCl)

was added to a suspension of 2-methyl-S-methyldithiocarbazate (73.39 mmol, 10 g) in toluene (80 ml). The mixture was stirred at reflux for 4h then allowed to cool down overnight. The solids were isolated by filtration, washed with water and then with ether to give 15 g of the expected 3-acyl-2-methyl-S-methyldithiocarbazate **(2a)**.

Yield= 74%

^{1}H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 7.65 (dd, 2H), 7.90 (dd, 2H), 11.68 (s, 1H).

Intermediate 2b: R2= methyl, R3= 4-(methylsulfonyl)-phenyl
_N'_-[1-(4-Methanesulfonyl-phenyl)-methanoyl]-_N_-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

The appropriate acyl chloride (1.68 mmol, 0.39 g) was added to a suspension of 2-methyl-S-methyldithiocarbazate (1.77 mmol, 0.24 g) in toluene (2 ml). After 5h at reflux, the mixture was cooled down overnight, triturated in ether and stirred over 2 h at RT to give 440 mg of the expected product **(2b)** as a white solid.

Yield= 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.5 (s, 3H), 3.30 (s, 3H), 3.65 (s, 3H), 8.15 (m, 4H), 11.9 (s, 1H).

Intermediate 2c: R2= methyl, R3= 4-cyano-phenyl
_N'_-[1-(4-Cyano-phenyl)-methanoyl]-N-methyl-hydrazinecarbodithioic acid methyl ester

The appropriate acyl chloride (22.77 mmol, 3.77 g) (R3COCl) was added to a suspension of 2-methyl-S-methyldithio carbazate (22.77 mmol, 3.10 g) in toluene (25 ml). The mixture was stirred at reflux for 3h-3h30 then allowed to cool down overnight. The solids were isolated by filtration, washed with water then with ether and dried to give 4.15 g of the expected 3-acyl-2-methyl-S-methyldithiocarbazate **(2c)**.

Yield= 68%

^{1}H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 8.05 (m, 4H), 11.85 (s, 1H).

Intermediate 2d: R2= methyl, R3= 4-acetyamino-phenyl
N'-(4-Acetylamino-benzoyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (10 mmol, 1.4 g) in toluene (30 ml), was added triethylamine (20 mmol, 2.8 ml) followed by 2-methyl-S-methyldithiocarbazate (12 mmol, 2.4 g). The mixture was maintained at 90°C for 2 hours and was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and washed with AcOEt to give 1.28 g of the title compound.

Yield= 45%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 7.85 (d, 2H), 7.90 (d, 2H), 10.30 (s, 1H), 11.40 (s, 1H).

Intermediate 2e: R2= methyl, R3= 4-acetylamino-3-pyridyl
N'-(6-Acetylamino-pyridine-3-carbonyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (63 mmol, 11 g) in toluene (150 ml) was added triethylamine (130 mmol) followed by 2-methyl-S-methyldithiocarbazate (62 mmol, 9 g). After 3h at room temperature, the mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (95:5 (dichloromethane (DCM)/MeOH) to give 9 g of the title compound.

Yield= 50%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 8.25 (m, 2H), 8.80 (s, 1H), 10.90 (s, 1H).
MS (m/z) / M+1= 298.99

Intermediate 3: PROTOCOL A

Intermediate 3a: R2= methyl, R3= 4-chloro-phenyl
1,3,4-Thiadiazolium, 5-(4-chlorophenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of the (2a) (54.4 mmol, 15 g) in ether (150 ml) at 0°C, acetic anhydride (30 ml) was added slowly and then $HClO_4$ 70% (65.33 mmol, 5.61 ml) was added dropwise at 0°C for 1 hour. The resultant mixture was stirred at RT overnight and the precipitate separated by filtration, was washed with ether and then air dried to give 19 g of the title compound (3a) as white solid.
Yield= 97%.
^{1}H-NMR (400MHz, DMSO) δ ppm: 2.92 (s, 3H), 3.99 (s, 3H), 7.52 (dd, 2H), 7.82 (dd, 2H).
MS (m/z) / M+1 = 257/259

Intermediate 3b : R2= methyl, R3= 4-(methylsulfonyl)phenyl
1,3,4 - Thiadiazolium, 5-(4-Methanesulfonyl-phenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of the (2b) (0.69 mmol, 0.22 g) in ether (3 ml) at 0°C, acetic anhydride (0.4 ml) was added slowly and then $HClO_4$ 70% (0.90 mmol, 0.080 mL) was added dropwise at 0°C for 1 hour. The resultant mixture was then allowed to rise to RT and stirred for 3h. The precipitate was isolated by filtration then air dried to give 220 mg of the expected 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate **(3b)** as a white solid.
Yield= 78%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.14 (s, 3H), 3.33 (s, 3H), 4.20 (s, 3H), 8.20 (dd, 2H), 8.25 (dd, 2H).
MS (m/z) / M+1 = 301/303

Intermediate 3c: R2= methyl, R3= 4-cyano-phenyl
1,3,4 - Thiadiazolium, 5-(4-cyanophenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of intermediate (2c) (15.64 mmol, 4.15 g) in ether (50 ml) and acetic anhydride (13.3 ml), $HClO_4$ 70% (18.76 mmol, 1.6 ml) was added dropwise at 0°C and stirred during 15-30 minutes at 0°C. The resultant mixture was stirred during 1H30 at room temperature and the precipitate, separated by filtration, was washed with ether and then air dried to give 5.22 g of the title compound (3c) as white solid.

Yield= 96%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.15 (s, 3H), 4.21(s, 3H), 8.15 (m, 4H).

Intermediate 3d: R2= methyl, R3= 4-acetylamino-phenyl
1,3,4-thiadiazolium, 5-(4-Acetylaminophenyl)-3-methyl-2-(methylthio)-trifluoromethanesulfonic acid

To a suspension of (2d) (4.3 mmol, 1.28 g) in dichloromethane (15 ml) was added trimethylsilyl trifluoromethane-sulfonate (12.9 mmol, 2.34 mL) dropwise. The resulting mixture was stirred overnight. The precipitate was isolated by filtration and then dried under reduced pressure to give 1.3 g of the expected 3-methyl-2-methylthio[1,3,4]thiadiazolium triflate (3d) as a white solid.

Yield= 72%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 3.10 (s, 3H), 4.15 (s, 3H), 7.80 (dd, 2H), 7.95 (dd, 2H), 10.40 (s, 1H).

Intermediate 3e: R2= methyl, R3= 4-acetylamino-3-pyridyl
1,3,4-thiadiazolium, 5-(6-acetylamino-pyridin-3-yl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of (2e) (3.4 mmol, 1 g) in ether (11 ml) was slowly added acetic anhydride (2 ml) followed by $HClO_4$ 70% (4 mmol, 0.7 g) dropwise at 0°C over 1 hour. The resulting mixture was then allowed to warm up to room temperature and stirred overnight. Additional $HClO_4$ 70% (0.7 mmol, 0.1g) was

added at 0°C and the mixture was stirred for 2h. The precipitate was isolated by filtration washed with AcOEt then dried under reduced pressure to give 1 g of the expected (3e).

Yield = 77%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 3.15 (s, 3H), 4.20 (s, 3H), 8.30 (dd, 1H), 8.40 (dd, 2H), 8.90 (d, H), 11.05 (s, 1H).

MS (m/z) / M+1 = 280.92

Compound I : PROTOCOL A

Example I1: R1= 3-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate **(3a)** (0.7 mmol, 0.25 g) in ethanol (3.5 ml), 3-aminobenzoic acid (1.05 mmol, 0.144 g) and triethylamine (0.7 mmol, 0.098 ml) were added, and the mixture was maintained at 70°C for 7 hours. On cooling to RT overnight, the solid formed was isolated by filtration to give 0.180 g of the expected compound.

Yield= 74.3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.30 (dd, 1H), 7.5 (dd, 1H), 7.54 (dd, 2H), 7.60 (s, 1H), 7.54 (dd, 1H), 7.71 (dd, 2H), 12.91-13.04 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ= 214 nm)= 99.03%

The following compounds were prepared by the procedure described in example **I.1** using appropriate intermediates and reagents. The desired products were obtained after purification by chromatography on silica gel.

I1.1	(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid

I1.2	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
I1.3	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-ethyl-phenyl)-amine
I1.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-pyrrolidin-3-yl-amine
I1.5	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N',N'-dimethyl-benzene-1,4-diamine
I1.6	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-6-methyl-benzoic acid
I1.7	2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
I1.8	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-ethyl-phenyl)-amine
I1.9	{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol

Example I1.10: R1= 3-carboxylic acid cyclohexyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid

Compound I1.10 was prepared by the procedure described in example I1 (3h at 75°C) using appropriate intermediates and reagents (protocol A).

The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography eluting with dichloromethane containing from 0 to 5% of methanol and then isocratic elution with DCM / MeoH (90/10).

Yield= 7.0%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.95-1.20 (m, 4H), 1.62-1.74 (m, 3H), 1.74-1.80 (m 1H), 2.10-2.13 (b, 1H), 2.39-2.48 (b, 1H), 2.84-2.90 (m, 1H), 3.10 (3H, s), 7.33 (dd, 2H), 7.44 (dd, 2H), 11.89-11.84 (b, 1H).

MS (m/z) / M+1 = 352/354

HPLC (uv purity, λ = 214 nm) = 97.61%

Example I2: R1= 2-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate **(3a)** (0.7 mmol, 0.25 g) in ethanol (3 ml), 2-aminobenzoic acid (0.84 mmol, 0.115 g) and triethylamine (0.7 mmol, 0.098 ml) were added, and the mixture was heated at 70°C for 7 hours. On cooling, the solid formed was filtered off to give 210 mg of the expected compound.

Yield= 87%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.20 (m, 1H), 7.2.8 (dd, 1H), 7.56-7.64 (m, 3H), 7.78 (dd, 2H), 7.95 (dd, 1H), 13.52-13.59 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ= 214 nm) = 97.64%

Example I2.1: R1= (4-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

Compound I2.1 was prepared by the procedure described in example I2 using appropriate intermediates and reagents (protocol A).

The precipitate obtained on cooling was washed with EtOH to give 0.250 g of the title compound.

Yield= 60%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.71 (s, 3H), 7.29-7.33 (m, 3H), 7.48-7.51 (m 1H), 7.54 (dd, 2H), 7.70 (dd, 2H), 13.27-13.29 (b, 1H).

MS (m/z) / M+1= 364/366

HPLC (uv purity, λ = 214 nm) = 95.77%

Example I2.2: R1= (2,4,5-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid

Compound I2.2 was prepared by the procedure described in example I2 using the appropriate intermediates and reagents. Acetonitrile was used as solvent and the reaction was warmed at 80°c for 24h (protocol A).

The solid formed after cooling was filtered off and washed with MeOH to give 0.250 g of the title compound.

Yield= 48.6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.74 (s, 3H), 7.44-7.54 (m, 1H), 7.55 (dd, 2H), 7.73 (dd, 2H), 14.15-14.30 (b, 1H).

MS (m/z) / M+1= 400/402

HPLC (uv purity, λ = 214 nm)= 95.82%

Example I3: R1= propyl, R2= methyl, R3= 4-chloro-phenyl
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.28 mmol, 0.10 g) in methanol (4 ml), propylamine (1.35 mmol, 0.115 ml) and triethylamine (0.28 mmol, 0.038 ml) were added, and the reaction was heated at 55°C for 5 hours. On cooling, the mixture was evaporated to dryness and the crude was chromatographed on silica gel (Alltech column, 2 g silica) with a mixture of cyclohexane:EtOAc (98:2) to give the expected compound.

Yield= 0.03g, 45.2%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.89 (t, 3H), 5.53-5.65 (m, 2H), 2.97 (t, 2H), 7.49 (dd, 2H), 7.62 (dd, 2H).

MS (m/z) / M+1= 268/270

HPLC (uv purity, λ= 214 nm)= 97.60%

The following compounds were prepared by the procedure described in example I3 using appropriate intermediates and reagents.

I3.1	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I3.2	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine
I3.3	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine
I3.4	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
I3.5	(4-Chloro-benzyl)-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I3.6	Benzyl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I3.7	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
I3.8	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine
I3.9	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-phenyl-propan-1-ol
I3.10	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol

The following compounds were prepared by the procedure described in example I3 using appropriate intermediates and reagents and with isopropanol as solvent.

I3.11	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
I3.12	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxymethyl-propane-1,3-diol
I3.13	tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.14	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-

	2-ylidene]-isopropyl-amine
I3.15	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I3.16	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine
I3.17	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I3.18	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
I3.19	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine
I3.20	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
I3.21	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3,4-dichloro-phenyl)-amine
I3.22	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-methoxy-phenyl)-amine
I3.23	(1R*,2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I3.24	N'-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N,N-dimethyl-ethane-1,2-diamine

Example I3.25: R1= (1R*, 2S*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I3.25 was prepared by the procedure described in example I3 (protocol A) with isopropanol as solvent.

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) eluting with dichloromethane containing from 0 to 1% methanol.

Yield= 0.015 g, 12%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.30 (b, 2H), 1.40-1.50 (b, 2H), 1.50-1.72 (b, 4H), 2.80-2.83 (b, 1H), 3.50 (s, 3H), 3.55-3.60 (b, 1H), 4.02-4.04 (b, 1H), 7.45 (d, 2H), 7.60 (d,

2H).
MS (m/z) / M+1= 324/3256
HPLC (uv purity, λ= 214 nm)= 96.62%

The following compound was prepared by the procedure described in example I3 with isopropanol as solvent.

I3.26	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine

Example I4: R1= 3-benzoic acid, R2= methyl, R3= 4-(methanesulfonyl)-phenyl

3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (0.547 mmol, 0.22 g) in ethanol (2.5 ml), 3-aminobenzoic acid (0547 mmol, 0.075 g) and triethylamine (0.601 mmol, 0.084 ml) were added, and the reaction was maintained for 6 hours at 75°C. On cooling overnight, the precipitate was filtered off, washed with ethanol then purified on silica gel, eluted with a gradient of DCM then DCM:MeOH (95:5) to give 70 mg of the expected compound.
Yield= 33%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.78 (s, 3H), 7.31 (dd, 1H), 7.54 (dd, 1H), 7.60 (s, 1H), 7.65 (s, 1H), 7.97 (dd, 2H), 8.03 (dd, 2H), 12.92-12.03 (b, 1H).
MS (m/z) / M+1= 390
HPLC (uv purity, λ= 214 nm)= 95.14%

The following compounds were prepared by the procedure described in example I4 with an excess of triethylamine (10eq) and of the appropriate amine (10eq). The reaction was refluxed for 5h.

I4.1	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopropyl-amine
I4.2	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-

	2-ylidene]-cyclohexylmethyl-amine

Example I5: R1= 3-hydroxyphenyl, R2= methyl, R3= 4-chlorophenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol

In this example, polystyrene morpholine resin was used to replace triethylamine and the isocyanate resin to remove the remaining amino derivative.

The suspension of morpholine resin (0.70 mmol, 0.20 g) and 3-aminophenol (0.84 mmol, 0.09 g) in ethanol (3.5 ml) was stirred at RT for 5 min before the addition of 1,3,4-thiadiazolium perchlorate **(3a)** (0.70 mmol, 0.25 g). After 5 hours at 70°C, the mixture was allowed to cool down before the filtration of the resin. The crude obtained after the evaporation of the solvent was purified on chromatography gel (Alltech column, 2 g silica) and eluted with gradient of DCM and MeOH:DCM (99:1) to give a mixture (0.07 g) of the remained amino derivative and the expected compound. To this mixture in DCM (7 ml) / MeOH (0.5 ml), was added the isocyanate resin (2.44 mmol, 2.00 g) and the suspension was stirred at RT overnight. After filtration of the resin, the filtrate was evaporated to dryness to give 30 mg of the pure product.

Yield= 13.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.68 (s, 3H), 6.45-6.51 (m, 3H), 7.13-7.19 (m, 1H), 7.55 (dd, 2H), 7.71 (dd, 2H), 9.40-9.48 (b, 1H).

MS (m/z) / M+1= 318/320

HPLC (uv purity, λ = 214 nm)= 98.44%

Example I6: R1= 4-hydroxy-3-benzoic acid, R2= methyl, R3= 4-chlorophenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid

The compound I6 was prepared by the procedure described in example I2 (protocol A). The precipitate obtained on cooling

was washed with DCM then purified by chromatography on silica gel (Alltech column, 5g silica) eluted with a mixture of DCM/MeOH from 100/0 to 85/15.

Yield= 17.0%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.07 (s, 1H), 3.59 (s, 3H), 6.70 (d, 1H), 6.93-6.98 (m 1H), 7.30 (s, 1H), 7.38-7.41 (m, 2H), 7.57-7.62 (m, 2H).

MS (m/z) / M+1= 362/364

HPLC (uv purity, λ= 214 nm)= 95.89%

The following compounds were prepared by the procedure described in example I6, using appropriate intermediates and reagents. Either morpholine resin or pyridine was used to replace triethylamine.

I6.1	(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.2	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-diethylaminomethyl-phenol
I6.3	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I6.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(2-ethyl-phenyl)-amine
I6.5	(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I6.6	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-methoxy-phenyl)-amine
I6.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine
I6.8	(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.9	{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
I6.10	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N',N'-dimethyl-benzene-

	1,3-diamine
I6.11	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide

Example I7: R1= Exo-2-norbornyl, R2= methyl, R3= 4-chloro-phenyl

Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine

The compound I7 was prepared by the procedure described in example I3 using appropriate intermediates and reagents(protocol A).

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) with a gradient of cyclohexane: EtOAc from 100: 0 to 97:3

Yield= 44.8 %

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.09-1.18 (b, 3H), 1.27-1.33 (b, 1H), 1.40-1.52 (b, 2H), 1.58-1.62 (m, 1H), 1.70-1.76 (m, 1H), 1.99-2.10 (b, 1H), 2.24-2.27 (b, 1H), 3.45 (s, 3H), 7.53 (d, 2H) 7.64 (d, 2H).

MS (m/z) / M+1= 320/322

HPLC (uv purity, λ= 214 nm)= 93.17%

Example I8: R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I8 was prepared by the procedure described in example I3 using appropriate intermediates and reagents(protocol A).

Triethylamine was replaced by morpholine resin (2.1 mmol, 0.61 g, loading 3.47 mmol/g); the mixture of morpholine resin and trans-2-aminocyclohexanol hydrochloride (2.1 mmol, 0.318 g) was stirred in ethanol (3.5 ml) at RT for 5 min before the addition of 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (**3a**) (0.7 mmol, 0.25 g). The residue was subjected to silica gel chromatography (Alltech column, 2g silica) eluting with

dichloromethane containing from 0 to 1% methanol.

Yield= 0.050g, 22%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.25 (m, 4H), 1.50-1.66 (m, 3H), 1.71-1.79 (b, 1H), 2.28-2.33 (m, 1H), 3.21-3.27 (m, 1H), 3.40 (s, 3H), 4.38 (s, 1H), 7.42 (dd, 2H), 7.54 (dd, 2H).

MS (m/z) / M+1= 324/326

HPLC (uv purity, λ= 214 nm)= 99.9%

The following compounds were prepared by the procedure described in example I8 using appropriate intermediates and reagents.

I8.1	5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
I8.2	3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
I8.3	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid
I8.4	(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine

Example I9: R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-(methanesulfonyl)-phenyl

(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I9 was prepared by the procedure described in example I4 (protocol A).

3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate **(3b)** (0.372 mmol, 0.15 g), trans-2-aminocyclohexanol hydrochloride (0.410 mmol, 0.062 g) and triethylamine (0.7814 mmol, 0.109 ml) were reacted in ethanol (1.5 ml). The crude was twice chromatographed on silica gel with a mixture of DCM: MeOH (98:2) to give the title product.

Yield= 0.030g, 23%

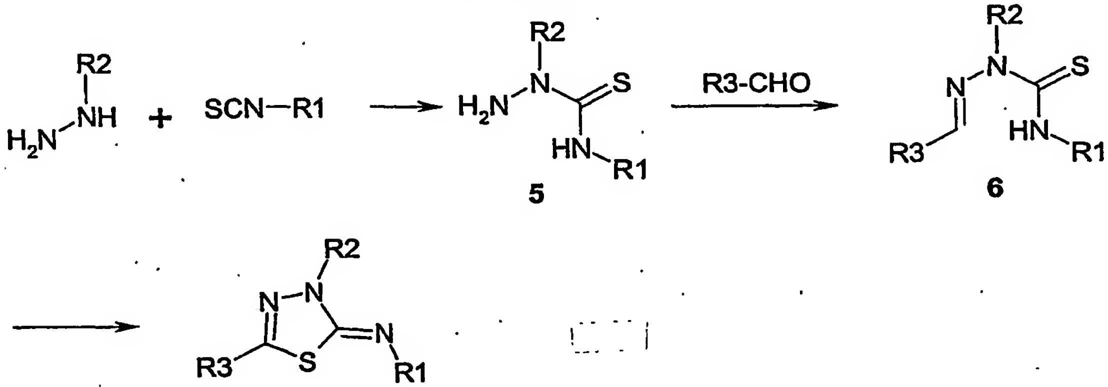
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.37 (m, 5H), 1.60-1.78

(b, 3H),1.81-1.90 (b, 1H), 3.3 (s, 3H), 3.32-3.40 (b, 1H), 3.52 (s, 3H), 4.53 (s, 1H), 7.89 (d, 2H), 8.01 (d, 2H).

MS (m/z) / M+1= 368/370

HPLC (uv purity, λ= 214 nm)= 99.17%

Protocol B



5

6

(I)

Intermediate 5 : PROTOCOL B

Intermediate 5a: R1= cyclohexyl, R2= methyl
Hydrazinecarbothioamide, N-(cyclohexyl)-1-methyl

The requisite cyclohexylisothiocyanate, (70.8 mmol, 10 g) was dissolved in methanol (35 ml) and this solution was added dropwise (30 min) to a stirred solution of methylhydrazine (134.5 mmol, 7 ml) in water (35 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 11.7 g of the expected derivative 5a.

Yield : 88.7%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m,5H), 1.50-1.60 (m,1H), 1.60-1.70 (m,2H), 1.80-1.90(m,2H), 3.40 (s,3H), 3.90-4.00 (m,1H), 4.80(s,2H), 7.85 (d,1H).

MS (m/z) / M+1 = 188,33

Intermediate 5b: R1= cyclohexyl, R2= H
Hydrazinecarbothioamide, N-cyclohexyl

The requisite cyclohexylisothiocyanate, (141 mmol, 20 ml)

was dissolved in methanol (30 ml) and this solution was added dropwise (35 min) to a stirred solution of hydrazinehydrate (423 mmol, 13.2 ml) in methanol (200 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 14.9 g of the expected derivative **(5b)**.

Yield: 61%

^{1}H-NMR(400MHz , DMSO) δ ppm : 1.10-1.35(m,5H), 1.50-1.60 (m,1H), 1.60-1.75(m,2H), 1.75-1.90 (m,2H), 4.00-4.10 (m,1H), 4.40 (s,2H), 7.50 (d,1H), 8.50 (s,1H).

MS (m/z) / M+1 =174,25

Intermediate 5c: R1= 3-benzoic-acid-methyl-ester, R2= H

Hydrazinecarbothioamide,N-(3-benzoic-acid-methyl-ester)

3-methoxycarbonylisothiocyanate(77.6 mmol, 15 g) was added dropwise (30 min) to a stirred solution of hydrazine hydrate (97 mmol, 4.7 mL) in methanol (40 mL) at -10°C. After stiring at -10°C for 5h, the solution was allowed to stir at room temperature overnight. The precipitate was filtered and washed with cold methanol to give 15.4 g of the expected compound (yield: 88%).

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.85 (s, 3H), 4.85 (brs, 1H), 7.43 (t, 1H), 7.68 (d, 1H), 7.87 (d, 1H), 8.33 (s, 1H), 9.23 (s, 1H).

MS (m/z) / M+1 = 226

Intermediate 6: PROTOCOL B

Intermediate 6a: R1=cyclohexyl, R2=methyl , R3= 2,4-dichlorophenyl

Hydrazinecarbothioamide, N-cyclohexyl-2-[(2,4-chlorophenyl)methylene]

A suspension of 2-methylthiosemicarbazide (5a) (2.67 mmol, 500 mg) in ethanol (5 ml) and 2,4-dichlorobenzaldehyde (2.94 mmol, 515 mg) were heated at 75°C for 18 hours. After cooling, the formed precipitate was filtered and washed with cold ethanol to give 876 mg of the title compound.

Yield: 95.3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m, 1H), 1.25-1.35 (m, 2H), 1.35-1.55 (m, 2H), 1.60-1.70 (m, 1H), 1.70-1.80 (m, 1H), 1.90-2.00 (m, 2H), 3.80 (s, 3H), 4.10-4.30 (m, 1H), 7.50 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.20 (d, 1H), 8.50 (d, 1H).

EXAMPLE I : PROTOCOL B

Example I10: R1= cyclohexyl, R2= methyl, R3= 2,4-dichlorophenyl

Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure described in example 6a) (2.3 mmol, 800 mg) was suspended in ethanol (5ml) and the oxidant $FeCl_3$,$6H_2O$ (5.06 mmol, 1.38 g) dissolved in ethanol (5 ml) was added. The mixture was heated at 75°C during 19h (TLC control). The oxidant (1.15 mmol, 0.31 g) was added to allow reaction to completion. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane starting with a ratio 5/95) to isolate 230 mg of the pure thiadiazoline. The byproduct mainly formed during this reaction is the 1,2,4-triazoline-5-thione.

Yield: 35%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H), 7.50 (d, 1H), 7.70-7.80 (m, 2H)

MS (m/z) / M+1= 344.1

HPLC (uv purity, λ= 214 nm): 99,9%

Example I10.1 : R1= cyclohexyl, R2= methyl, R3= 2-chloro-

phenyl

[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I10.1 was prepared by the procedure described in I10 using appropriate intermediates and reagent. The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.70 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.40-7.50 (m, 2H), 7.60 (d, 1H), 7.70 (d, 1H)

MS (m/z) / M+1= 310.2

HPLC (uv purity, λ= 214 nm): 99.9%

Example I11: R1= cyclohexyl, R2= methyl, R3= 4-(trifluoromethyl)-phenyl

Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure described in example 6a) (2 mmol, 700 mg) was suspended in ethanol (5 ml) and the oxidant $FeCl_3$, $6H_2O$ (4.4 mmol, 1.21 g) dissolved in ethanol (5 mL) was added. The mixture was heated at 75°C during 19h. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane as eluent with a rapport 5/95) to isolate 290 mg the pure thiadiazoline.

Yield:42%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.50 (m, 5H), 1.60-1.70 (m, 1H),1.75-1.90 (m, 4H),2.65-2.75 (m, 1H), 3.60 (s, 3H), 7.85-7.95 (m, 4H)

MS (m/z) / M+1= 342.6.

HPLC (uv purity, λ= 214 nm): 99.9%

Example I12: R1= cyclohexyl, R2= methyl, R3= 4-pyridyl
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compound I12 was prepared by the procedure described in example I11 using appropriate intermediates and reagents (protocol B).

The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluent: cyclohexane/ethyl acetate, 95/5).

Yield: 80%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H), 7.60 (d, 2H), 8.65 (d, 2H)

MS (m/z) / M+1= 275.2

HPLC (uv purity, λ= 214 nm): 99.9%

Example I13: R1= cyclohexyl, R2= methyl, R3= 3-chloro-phenyl
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compounds I13 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 23%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H), 7.45-7.55 (m, 2H), 7.55-7.65 (m, 1H), 7.70 (s, 1H)

MS (m/z) / M+1= 308

HPLC (uv purity, λ= 214 nm): 99.9%

Example I14: R1= cyclohexyl, R2= methyl, R3= 4-cyano-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

Compounds I14 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 8% AcOEt.

Yield: 10%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.80 (d, 2H), 7.90 (d, 2H)

MS (m/z) / M+1= 299.2

HPLC (uv purity, λ= 214 nm): 99.3%

Example I15 : R1= cyclohexyl, R2= methyl, R3= 4-methylsulfonyl-phenyl
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compounds I15 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 10% AcOEt. Protocol D gave better yield to prepare I15.

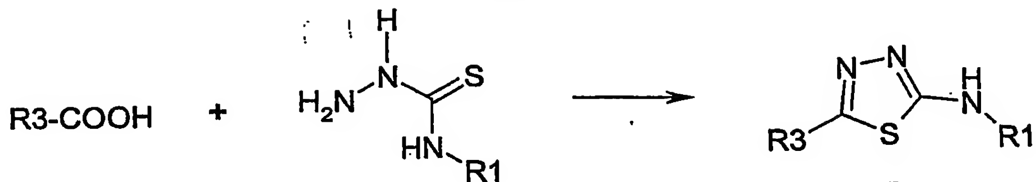
Yield: 3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.20 (s, 3H), 3.45 (s, 3H), 7.80 (d, 2H), 7.90 (d, 2H).

MS (m/z) / M+1= 352.5

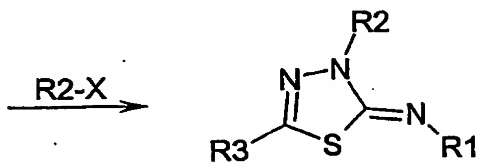
HPLC (uv purity, λ= 214 nm): 87.3%

Protocol C



5'

7



(I)

Intermediate 7: PROTOCOL C

Intermediate 7a: R1= cyclohexyl, R3= 4-chloro-3-sulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a mixture of 4-chloro-3-sulfamoyl-benzoic acid (6.36 mmol, 1.5 g), thiosemicarbazide (5b) (6.36 mmol, 1.10 g) in dioxane (40 ml) at 60°C, $POCl_3$ (6.36 mmol, 600 μl) was added and the mixture was warmed at reflux for 2h30 and 16h at RT. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with a solution of diluted NH_4OH. The yellow precipitate obtained was collected by filtration, washed with water before drying under vacuum over P_2O_5 to give 2g of the desired product.

Yield = 84 % ;

^1H (400MHz, DMSO) δ ppm : 1.10-1.37 (m, 5H), 1.55 (m, 1H), 1.70 (m, 2H), 1.98 (m, 2H), 3.55 (m, 1H), 7.66-7.82 (m, 3H), 7.90 (m, 1H) ; 8.25-8.37 (br, 2H).

MS (m/z) / M+1 = 373/375

Intermediate 7b: R1= cyclohexyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl

2,4-Dichloro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a mixture of 2,4-dichlorobenzoic acid (1.85 mmol, 500 mg), thiosemicarbazide (5b) (1.85 mmol, 320 mg) in anhydrous dioxane (10 mL) at 70-80°C, $POCl_3$ (1.85 mmol, 173 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and purified by silica gel chromatography using cyclohexane/ethyl acetate as eluent to give 351mg of the title compound.

Yield: 46.3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.65 (m, 1H), 1.65-1.80 (m, 2H), 1.90-2.05 (m, 2H), 3.50-3.70 (m, 1H), 7.85 (d, 2H), 8.05 (s, 1H), 8.20-8.40 (m, 1H), 8.60 (s, 1H).

MS (m/z) / M+1= 407.1

HPLC (uv purity, λ= 214 nm): 97.1%

Intermediate 7c: R1= cyclohexyl, R3= 3-thienyl
Cyclohexyl-(5-thiophen-3-yl-[1,3,4]thiadiazol-2-yl)-amine

To a mixture of 3-thiophenecarboxylic acid (3.9 mmol, 500 mg), thiosemicarbazide **5b** (3.9 mmol, 675 mg) in anhydrous dioxane (10 ml) at 60-65°C, $POCl_3$ (5 mmol, 473 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration and washed with water. The solid was then dried under vacuum to provide 965 mg of the desired compound **(7c)**.

Yield : 93%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75(m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55 (m, 1H), 7.45 (d, 1H), 7.65 (d, 1H), 7.80 (d, 1H), 7.85 (s, 1H).

Intermediate 7d: R1= cyclohexyl, R3= 3-chloro-2,6-dimethoxyphenyl

[5-(3-Chloro-2,6-dimethoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-chloro-2,6-dimethoxybenzoic acid (2.3 mmol, 500 mg), thiosemicarbazide **5b** (2.3 mmol, 399 mg) in anhydrous dioxane (10 ml) at 70-80°C, $POCl_3$ (2.3 mmol, 215 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was subjected to flash chromatography eluting with ethyl acetate/cyclohexane to give 115 mg of the title compound.

Yield: 14%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 2H), 1.95-2.05 (m, 2H), 3.50-3.60 (m, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.55 (d, 1H), 7.75(d, 1H).

MS (m/z) / M+1 = 354.1

Intermediate 7e: R1= cyclohexyl, R3= 3-bromo-4-methoxyphenyl
[5-(3-Bromo-4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-bromo-4-methoxybenzoic acid (2.16 mmol, 500 mg), thiosemicarbazide **5b** (2.16 mmol, 375 mg) in anhydrous dioxane (10 ml) at 60-65°C, $POCl_3$ (2.8 mmol, 262 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was solubilized in 50 ml of dichloromethane/methanol (7/3) to which was additionned a morpholine resin (13.88 mmol, 4 g). The mixture was stirred overnight to remove the excess of acid. The resin morpholine salt was filtered and the organic layer was concentrated by distillation under reduced pressure to give 740 mg of the

purified product (7e).

Yield: 92.8%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55 (m, 1H), 7.45 (dd, 1H), 7.65 (dd, 1H), 7.80 (dd, 1H), 7.85 (dd, 1H).

Intermediate 7f: R1= cyclohexyl, R3= 2-pyrazinyl

Cyclohexyl-(5-pyrazin-2-yl-[1,3,4]thiadiazol-2-yl)-amine

To a mixture of 2-pyrazine carboxylic acid (2.885 mmol, 0.358 g), thiosemicarbazide (5b) (2.885 mmol, 0.5 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was then basified to pH 7 with a saturated solution of sodium bicarbonate then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated to dryness to give the expected product.

Yield= 0.6 g, 79.6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.44 (m, 5H), 1.56-1.63 (b, 1H), 1.70-1.77 (b, 2H), 2.00-2.05 (b, 2H), 3.60-3.68 (b, 1H), 8.22 (d, 1H), 8.67-8.69 (m, 2H), 9.28 (s, 1H).

Intermediate 7g: R1= cyclohexyl, R3 =3,4-dihydroxyphenyl

4-(5-Cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol

To a mixture of 3,4-dihydroxybenzoic acid (2.885 mmol, 0.445 g), thiosemicarbazide (5b) (2.885 mmol, 0.500 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was basified with a saturated solution of sodium bicarbonate to pH 7 then stirred at RT overnight. The precipitate was filtered, washed with hexane then dried to give the title compound.

Yield: 71%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.39 (m, 5H), 1.55-1.62 (b, 1H), 1.70-1.78 (b, 2H), 1.95-2.00 (b, 2H), 3.48-3.53 (b, 1H), 6.80 (d, 1H), 6.98 (d, 1H), 7.19 (s, 1H), 7.68 (d, 1H), 9.20-9.40 (b, 2H).

Intermediate 7h: R1 = cyclohexyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

Thiosemicarbazone (6b) (obtained from 5b following the protocol 6a) (10 mmol, 3 g) was suspended in ethanol (50 ml) and the oxidant $FeCl_3,6H_2O$ (23 mmol, 6.3 g) was added. The mixture was heated at reflux for 3h. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The organic layer was washed with water, dried under magnesium sulphate, filtered, and distilled to give a residue submitted to another oxidative process with $FeCl_3$, $6H_2O$ (3 g) in ethanol (50 ml). The mixture was heated at reflux for 3h and 12h at RT. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was triturated and wash with cyclohexane to give 2.5g of the title product.

Yield: 85%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.95-1.22 (m, 5H), 1.35-1.45 (b, 1H), 1.50-1.60 (m, 2H), 1.80-1.87 (m, 2H), 3.32-3.42 (b, 1H), 7.35 (d, 2H), 7.55 (d, 2H), 7.75 (d, 1H)

MS (m/z) / M+1 = 294.1

HPLC (uv purity, λ= 214 nm): 97.21%

Intermediate 7i: R1= cyclohexyl, R3= 3-chloro-4-hydroxy-5-methoxyphenyl

2-chloro-4-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol

To a mixture of 3-chloro-4-hydroxy-5-methoxybenzoic acid (2.468 mmol, 500 g), thiosemicarbazide (5b) (2.468 mmol, 427 mg) in dioxane (10 ml) at 65°C, $POCl_3$ (3.2 mmol, 300 μl) was added and the mixture was warmed at 95°C for 3h30. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with a solution of diluted NH_4OH. The precipitate obtained was collected by

filtration, washed with water before drying under vacuum over P_2O_5 to give 675 mg of the desired product.
Yield = 80%

^{1}H-NMR (400MHz, DMSO)δ ppm: 1.15-1.36 (m, 5H), 1.53-1.63 (m, 1H), 1.67-1.80 (m, 2H), 1.95-2.05(m, 2H), 3.45-3.57 (m, 1H), 3.90 (s, 3H), 7.25 (s, 1H) ; 7.30 (s, 1H), 7.85 (d, 1H), 9.90 (s, 1H)

Intermediate 7j: R1= 3-benzoic-acid-methyl-ester, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-[1,3,4]thiadiazol-2-ylamino]-benzoic acid methyl ester

To a mixture of 3-cyanobenzoic acid (2.92 mmol, 0.43 g), (5c)(3 mmol, 0.7 g) in dioxane (10 mL) at 85°C, $POCl_3$ (3.8 mmol, 350 µL) was added and the mixture was heated at 95°C for 3h30. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed successively with water and with ether before being dried under vacuum to give 0.5 g of the desired product (yield: 49%).

^{1}H-NMR (400 MHz, DMSO)δ ppm: 3.88 (s, 3H), 7.53 (t, 1H), 7.63 (d, 1H), 7.72 (t, 1H), 7.86 (d, 1H), 7.96 (d, 1H), 8.23 (d, 1H), 8.32 (s, 1H), 8.43 (s, 1H), 10.89 (s, 1H).
MS (m/z) / M+1 = 337

Intermediate 7k: R1= 3-benzoic-acid-methyl-ester, R3= 2-pyridyl

3-(5-Pyridin-2-yl-[1,3,4]thiadiazol-2-ylamino)-benzoic acid methyl ester

To a mixture of picolinic acid (2.92 mmol, 0.36 g), (5c) (3 mmol, 0.7 g) in dioxane (10 ml) at 85°C, $POCl_3$ (3.8 mmol, 350 µL) was added and the mixture was heated at 95°C for 5h. The solvent was removed by distillation under reduced pressure to give a crude material. Methanol was added and the precipitate obtained was collected by filtration, washed with methanol and dried under vacuum to give 0.59 g (61%) of

the desired product. The crude material was engaged in the next step without purification.

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.5 (m, 2H), 7.6 (d, 1H), 7.88 (d, 1H), 7.98 (t, 1H), 8.12 (d, 1H), 8.42 (s, 1H), 8.63 (d, 1H), 10.9 (s, 1H).

MS (m/z) / M+1 = 313/314/315

EXAMPLE I : PROTOCOL C

Example I16: R1= cyclohexyl, R2= methyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl

2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a solution of 1,3,4-thiadiazole **7b** (0.195 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.23 mmol, 27 μl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.527 mmol (64 μl) of methyltrifluoromethane sulfonate to allow reaction to completion, and 0.585 mmol (82 μl) of triethylamine. The filtrate is concentrated by distillation under reduced pressure. The product was purified via column chromatography on silica gel (eluted with cyclohexane/ethyl acetate, 80/20) to give 48 mg of the title product.

Yield: 58%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.80 (d, 2H), 8.0 (s, 1H), 8.35 (s, 1H).

MS (m/z) / M+1: 421.3

HPLC (uv purity, λ= 214 nm): 99.4%

Example I17: R1= cyclohexyl, R2= methyl, R3= 3-thienyl

Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine

To a solution of 1,3,4-thiadiazole **7c** (0.75 mmol, 200 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (1.13 mmol, 128 μl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.225 mmol (26

μl) of methyltrifluoromethanesulfonate to allow reaction to completion, and 0.675 mmol (94 μl) of triethylamine. The mixture is concentrated by distillation under reduce pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution with ethyl acetate. The organic layer was saturated with NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography, eluting with cyclohexane containing from 0 to 15% AcOEt to provide 80 mg of the desired product.

Yield : 38%

^{1}H-NMR (400MHz , DMSO): δ ppm= 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.7-1.8 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.40 (d, 1H), 7.70 (d, 1H), 7.85 (s, 1H).

MS (m/z) / M+1= 280.23

HPLC (uv purity, λ= 214 nm): 99.9%

Example I17.1: R1= cyclohexyl, R2= methyl, R3= 3,5-dichloro-phenyl

Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I17.1 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.

Yield: 43%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.90 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.65 (s, 2H), 7.70 (s, 1H)

MS (m/z) / M+1= 342.2

HPLC (uv purity, λ = 214 nm): 99.9%

Compound I17.2 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.

I17.2	Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Example I18: R1= cyclohexyl, R2= methyl, R3= 3-chloro-2,6-

dimethoxyphenyl

[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of the 1,3,4-thiadiazole **7d** (0.226 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoro methanesulfonate (0.27 mmol, 31 μl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.068mmol (7 μl) of methyltrifluoromethanesulfonate to allow reaction to completion. The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography. (eluent: cyclohexane/ethyl acetate, 80/20). 11 mg of desired product was obtained.

Yield: 13%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.50 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.60 (d, 1H)

MS (m/z) / M+1= 368.26

HPLC (uv purity, λ= 214 nm): 99.7%

Compound I18.1 was prepared by the procedure described in example I18 using appropriate intermediates and reagents:

I18.1	Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Example I18.2: R1= cyclohexyl, R2= methyl, R3= 2-(5-pyridin-2-yl)-thienyl

Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I18.2 was prepared by the procedure described in example I18 using appropriate intermediates and reagents. The residue was purified by silica gel chromatography

eluting with a gradient of cyclohexane containing from 0 to 10% ethyl acetate.

Yield: 57%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.30 (m, 1H), 7.35 (d, 1H), 7.80 (d, 1H), 7.85 (m, 1H), 7.95 (d, 1H), 8.55 (d, 1H).

MS (m/z) / M+1= 357.3

HPLC (uv purity, λ= 214 nm): 99.5%

Example I18.3: R1= cyclohexyl, R2= methyl, R3= 3,5-dihydroxy-4-methoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid

Compound I18.3 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described in example I18. In this particular case, the mixture was concentrated and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 45%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1-1.40 (m, 5H), 1.45-1.55 (m, 1H), 1.65-1.75 (m, 2H), 1.85-1.95 (m, 2H), 3.05-3.20 (m, 1H), 3.6 (s, 3H), 4.00 (bs, 3H), 6.65 (s, 2H), 9.60 (bs, 2H), 10.00 (bs, 1H).

MS (m/z) / M+1= 336.4

HPLC (uv purity, λ= 214 nm): 99.7%

Example I18.4: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4,5-dimethoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol;compound with trifluoro-methanesulfonic acid

Compound I18.4 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described example I18. In this particular case, the mixture was concentrated

and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 11%

1H-NMR (400MHz , DMSO) δ ppm: 1.10-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.85 (m, 2H), 1.95-2.10 (m, 2H), 3.10-3.25 (m, 1H), 3.75 (s, 3H), 3.85 (s, 6H), 6.85 (s, 1H), 6.95 (s, 1H), 9.80 (bs, 1H), 9.90 (bs, 1H).

MS (m/z) / M+1= 350.45

HPLC (uv purity, λ= 214 nm): 99.9%

Example I18.5: R1= cyclohexyl, R2= methyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I18.5 was prepared by the procedure described in example I18 using appropriate intermediates and reagents.

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.57-1.63 (m, 1H), 1.70-1.82 (m, 4H), 2.60 (br, 1H), 3.50 (s, 3H), 7.52(d, 2H), 7.65 (d, 2H).

MS (m/z) / M+1= 308/310

HPLC (uv putrity, λ= 214nm): 94.24%

Example I18.6: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-hydroxy-5-methoxy-phenyl

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compound I18.6 was prepared from the appropriate 1,3,4-thiadiazole 7i.To a solution of **intermediate 7i** (2 mmol, 675 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (3 mmol, 337 μl) was added. The resultant mixture was stirred for 48 h to give a precipitate. The mixture was filtered and washed with ethyl acetate to give 400 mg of desired product as a salt of trifluoromethanesulfonic acid.

Yield: 40%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

(m, 1H), 1.76-1.88 (m, 2H), 2.00-2.11 (m, 2H), 3.11-3.25 (m, 1H), 3.85 (s, 3H), 3.95 (s, 3H), 7.30 (s, 1H), 7.48 (s, 1H), 9.90 (s, 1H), 10.50 (s, 1H).

MS (m/z) / M+1= 354/356

HPLC (uv purity, λ= 214 nm): 99.4%

Example I19: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-sulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a solution of 1,3,4-thiadiazole **7a** (0.215 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.257 mmol, 29 µl) was added. The resultant mixture was stirred for 24 h. To this solution was added (0.065 mmol, 7 µl) of methyltrifluoromethanesulfonate to allow reaction to completion. The filtrate is concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography.(eluted with a gradient of cyclohexane/ethyl acetate) to afford 59 mg of pure product.

Yield: 71%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.25-1.55 (m, 5H), 1.65-1.75 (m, 1H), 1.75-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.65 (s, 3H), 7.80-7.95 (m, 4H), 8.30 (dd, 1H).

MS (m/z) / M+1: 387.3

HPLC (uv purity, λ= 214 nm): 99.7%

Example I19.1: R1= cyclohexyl, R2= methyl, R3= 4-chloro- N,N-diethyl-3-sulfonamide-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide

To a mixture of compound I19 (0.258 mmol, 0.100 g), tetra-n-

butylammonium hydrogen sulphate (0.0258 mmol, 0.090 g), 50% aqueous sodium hydroxide (0.300 ml) and toluene (2.2 ml), was added ethylbromide (0.310 mmol, 0.023 ml). The reaction was stirred at RT for 2h and then heated to 90°C for 1h30 before a second addition of ethylbromide (0.310 mmol, 0.023 ml). The mixture was heated at 90°C for 2h30 and the volatiles were removed by distillation. The crude material was solubilized with ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 0.1 g of the expected product as a white solid.

Yield= 87.7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.00 (t, 6H), 1.10-1.32 (b, 5H), 1.48-1.54 (m, 1H), 1.65-1.73 (b, 4H), 2.53-2.62 (b, 1H), 3.20-3.30 (m, 4H), 3.48 (s, 3H), 7.68-7.79 (m, 2H), 8.11 (s, 1H).

MS (m/z) / M+1= 443/445

HPLC (uv purity, λ= 214 nm)= 99.72%

Example I19.2: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl

{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine

To a solution of I19 (0.516 mmol, 0.2 g) in DMF (13 ml) were added potassium carbonate (1.548 mmol, 0.214 g) and water (3 ml). The mixture was stirred at RT until obtaining an homogenous solution and then the bis-(2-chloro-ethyl)methyl-amine hydrochloride (0.516 mmol, 0.10 g) was added. After a day of stirring, the mixture was warmed at 80°C for 15h. The solvents were then evaporated and the crude material was solubilized in dicloromethane. The organic layer was washed with a satured solution of bicarbonate of sodium, then with brine. After fitration, the filtrate was dried over $MgSO_4$ and concentrated by distillation. The crude material was chromatographed on silica gel, eluting with dichloromethane containing from 0 to 5% methanol. The solid product was then washed with ethyl acetate.

Yield= 10%

^{1}H-NMR (400MHz, $CDCl_3$ + D_2O) δ ppm: 1.20-1.48 (m, 5H), 1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.45 (s, 3H), 2.45 (t, 4H), 2.55-2.65 (m, 1H), 3.33 (t, 4H), 3.60 (s, 3H), 7.52 (d, 1H), 7.72 (d, 1H), 8.24 (s, 1H).

MS (m/z) / M+1= 470

HPLC (uv purity, λ= 214 nm): 99.53%

Example I19.3: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-[(pyridin-4-ylmethyl)-sulfamoyl]-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide

To a mixture of I19 (0.258 mmol, 0.1 g), triethylamine (0.516 mmol, 0.072 ml) and acetic acid (0.516 mml, 0.03 ml) in 1,2-dichloroethane, 4-pyridine carboxaldehyde (0.387 mmol, 0.037 ml) was added. The mixture was cooled to 0°C and sodium triacetoxyborohydride (0.516 mmol, 0.135 g) was added. After 24h of stirring at RT the same quantities of borohydride and aldehyde were added and the reaction was stirred for 15h.

The mixture was then filtered and the filtrate was diluted with dichloromethane, washed with water, brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was purified on silica gel eluting with dichloromethane containing from 0 to 7% of methanol. The solid product was then washed with ether to give the title product.

Yield= 40%

^{1}H-NMR (400MHz , DMSO) δ ppm:1.15-1.39 (m, 5H), 1.54-1.60 (m, 1H), 1.70-1.80 (m, 4H), 2.60-2.67 (m, 1H), 3.50 (s, 3H), 4.18 (s, 2H), 7.22 (d, 2H), 7.67 (dd, 1H), 7.76 (dd, 1H), 8.06 (d, 1H), 8.39 (d, 2H), 8.73-8.78 (b, 1H).

MS (m/z) / M+1= 478

HPLC (uv purity, λ= 214 nm): 99.99%

Example I19.4: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(2-morpholin-4-yl-ethyl-sulfamoyl)-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-

benzenesulfonamide

2-Chloro-*N*-(2-chloro-ethyl)-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide was prepared by the procedure described in example I19.3 using an appropriate aldehyde and I19. The residue was purified by silica gel chromatography eluting with a gradient cyclohexane containing from 0 to 20% of ethyl acetate followed by an isocratic elution with ethyl acetate/cyclohexane (4/6).

Yield= 84%

To a mixture of this intermediate (0.866 mmol, 0.390 g), in presence of sodium iodide in ethanol (10 ml), morpholine (8.66 mmol, 0.756 ml) was added. After 15 h at reflux, the mixture was evapored to dryness and the crude material was basified with a saturated solution of sodium bicarbonate. After extraction with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% of ethyl acetate.

Yield= 65%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.61-1.69 (m, 1H), 1.80-1.89 (b, 4H), 2.30-2.39 (m, 4H), 2.41-2.49 (m, 2H), 2.59-2.68 (m, 1H), 3.00-3.09 (m, 2H), 3.60-3.73 (m, 7H), 5.81-5.89 (b, 1H), 7.54 (d, 1H), 7.73 (d, 1H), 8.32 (s, 1H).

MS (m/z) / M+1= 500/501

HPLC (uv purity, λ= 214 nm): 97.76%

Example I19.5: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-ethylsulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.3. In this particular case, a large excess of acetaldehyde (20 equivalents) and triacetoxy borohydride (4 equivalents) were used and added once.

Yield= 50%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.13 (t, 3H), 1.22-1.50 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.87 (b, 4H), 2.57-2.64 (m, 1H), 2.97-3.04 (q, 2H), 3.60 (s, 3H), 4.90 (t, 1H), 7.53 (d, 1H), 7.77 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 415/416

HPLC (uv purity, λ= 214 nm): 99.36%

Example I19.6: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[ethyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

To a mixture of I19.4 (0.100 mmol, 0.05 g), N-tetrabutyl ammonium hydrogen sulfate (0.02 mmol, 0.008 g), a solution of 50% of sodium hydroxide (1.25 mmol, 0.1 ml) in toluene (2 ml), ethylbromide (1 mmol, 0.075 ml) was added. The mixture was heated to 90°C for 5h and then evaporated to dryness. The residue was solubilized in ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$, filtered and then distilled under vaccum. The crude material was purified on silica gel chromatography eluting with a mixture of ethylacetate/cyclohexane in a ratio 1/9 then 2/8 to give the expected product.

Yield= 60%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.13 (t, 3H), 1.22-1.45 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.84 (b, 4H), 2.38-2.43 (m, 4H), 2.50-2.53 (t, 2H), 2.57-2.64 (m, 1H), 3.40-3.50 (m, 4H), 3.60-3.65 (m, 7H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1 = 528/529

HPLC (uv purity, λ= 214 nm): 98.57%

Example I19.7: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[isopropyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

The title compound was prepared as described in example I19.6 with 13 equivalents of isopropylbromide. The residue was

purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 74%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.50 (d, 6H), 1.22-1.47 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.83 (b, 4H), 2.44-2.50 (m, 4H), 2.57-2.63 (m, 3H), 2.47-2.51 (t, 2H), 3.60 (s, 3H), 3.68-3.70 (m, 4H), 3.98-4.04 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 542/543
HPLC (uv purity, λ= 214 nm): 96.86%

Example I19.8: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-{ethyl-[2-(2-methoxy-ethoxy)-ethyl]-sulfamoyl}-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide

To a solution of I19.5 (0.241 mmol, 0.1 g) in EtOH (4 ml), potassium carbonate (0.289 mmol, 0.040 g) was addedd and then the reaction mixture was heated at reflux for 30 min before the addition of 1-bromo-2-(2-methoxyethoxy)ethane (0.289 mmol, 0.040 ml). After 3h at reflux, 2.4 equivalents of the bromo derivative were added and the mixture was kept at reflux for additional 15h. The mixture was then evaporated to dryness and the residue was diluted in water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 10 to 60% ethylacetate.
Yield= 64%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.11 (t, 3H), 1.20-1.47 (m, 5H), 1.61-1.68 (m, 1H), 1.79-1.89 (b, 4H), 2.59-2.68 (m, 1H), 3.36 (s, 3H), 3.43-3.50 (m, 4H), 3.54-3.58 (m, 4H), 3.61-3.65 (m, 5H), 7.50 (d, 1H), 7.70 (d, 1H), 8.28 (s, 1H).
MS (m/z) / M+1= 518/520
HPLC (uv purity, λ= 214 nm): 99.9%

Example I19.9: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(3-dimethylamino-2-hydroxy-propyl)-ethyl-sulfamoyl]-phenyl C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide

An excess of epibromohydrin (3 molar equivalents) was reacted with I19.5 following the procedure described in example I19.8. The intermediate was isolated by chromatography on silica gel eluting with a mixture of cyclohexane/ethylacetate in a ratio 1/9. To a solution of this intermediate (0.106 mmol, 0.05 g) in EtOH (2 ml) at 50°C, dimethylamine (0.318 mmol, 0.041 ml) was added and the mixture was heated at 70°C for 15h. The solvent was then removed under reduced pressure. The residue was diluted in water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and the volatile was evaporated to give the desired product.

Yield= 64%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H), 1.60-1.70 (m, 1H), 1.79-1.89 (b, 4H), 2.254-2.36 (m, 8H), 2.58-2.66 (m, 1H), 3.31-3.34 (dd, 1H), 3.42-3.60 (m, 6H), 3.79-3.87 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 516/517

HPLC (uv purity, λ= 214 nm): 96.60%

Example I19.10: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2,3-dihydroxy-propyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.8 with 3 eq. of 3-bromo-1,2-propane-diol and the reaction mixture was heated at reflux for 12h. The desired product was obtained after purification of the crude material by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 3% methanol.

Yield= 38%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H), 1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.17-2.22 (m, 1H), 2.59-2.66 (m, 2H), 3.40-3.48 (m, 3H), 3.51-3.57 (dd, 1H), 3.61 (s, 3H), 3.89-3.94 (m, 1H), 7.53 (d, 1H), 7.73 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 489/490
HPLC (uv purity, λ= 214 nm): 98.41%

Example I19.11: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[ethyl-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide

The title compound was prepared as described in example I19.9 using the same intermediate and pyrrolidine (3eq) as nucleophile. The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 2 to 3% of methanol.
Yield= 27%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.19-1.47 (m, 5H), 1.64-1.70 (m, 1H), 1.77-1.90 (m, 4H), 2.48-2.51 (dd, 1H), 2.53-2.78 (m, 7H), 3.33-3.37 (dd, 1H), 3.45-3.54 (m, 2H), 3.56 (d, 2H), 3.61 (s, 3H), 3.87-3.95 (m, 1H), 7.51 (d, 1H), 7.72 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 542/543
HPLC (uv purity, λ= 214 nm): 95.50%

Example I19.12: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-diethylamino-ethyl)-ethyl-sulfamoyl]-phenyl
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.8 using 3.3 eq of potassium carbonate and 2eq of 2-diethylaminoethylchloride hydrochloride. The residue was purified by silica gel chromatography eluting with a mixture

of MeOH/DCM (10/90).

Yield= 32%

^{1}H-NMR (400MHz,CDCl3) δ ppm: 1.00 (t, 6H), 1.17 (t, 3H), 1.22-1.48 (m, 5H), 1.61-1.70 (b, 1H), 1.80-1.90 (m, 4H), 2.48-2.53 (q, 4H), 2.59-2.63 (m, 3H), 3.40-3.45 (m, 4H), 3.63 (s, 3H), 7.50 (d, 1H), 7.72 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 514/ 515

HPLC (uv purity, λ= 214 nm): 99.34%

Example I19.13: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-dimethylamino-1-methyl-ethyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-methyl-ethyl)-N-ethyl-benzenesulfonamide (minor isomer) and Example I19.14: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-dimethylamino-propyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide (major isomer)

The title compounds were prepared by the procedure described in example I19.8 using 3.3 eq of potassium carbonate and 2eq of the of 2-dimethylaminoisopropylchloride hydrochloride. Two "isomers" were obtained from this reaction:

The crude material was purified by silica gel chromatography eluting with dichloromethane/methanol (99/1) to afford two isomers.

The minor isomer:

Yield= 10%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.20-1.47 (m, 11H), 1.64-1.72 (m, 1H), 1.77-1.86 (m, 4H), 2.10 (s, 6H), 2.23-2.36 (m, 2H), 2.54-2.66 (m, 1H), 3.31-3.39 (m, 1H), 3.42-3.52 (m, 1H), 3.59 (s, 3H), 3.88-3.93 (m, 1H), 7.50 (d, 1H), 7.70 (d, H), 8.30 (s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (uv purity, λ= 214 nm): 98.67%

The major isomer:

Yield= 30%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 0.92 (d, 3H), 1.11 (t, 3H), 1.23-1.50 (m, 5H), 1.62-1.70 (m, 1H), 1.79-1.89 (m, 4H), 2.14 (s, 6H), 2.59-2.64 (m, 1H), 2.77-2.86 (m, 1H), 3.33-3.51 (m, 4H), 3.59 (s, 3H), 7.50 (d, 1H), 7.70 (d, H), 8.30 (s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (uv purity, λ= 214 nm): 99.67%

Example I20: R1= cyclohexyl, R2= methylacetate, R3= 4-chlorophenyl

[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole **7h** (0.34 mmol, 100 mg) in anhydrous dioxane (3mL), an excess of methyl bromoacetate (3.4 mmol) was added. The resultant mixture was stirred for 48 h at 90°C. The mixture was concentrated and a saturated solution of K_2CO_3 was added. The solution was extracted with ethylacetate, the organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by chromatograpy on silica gel using a gradient of solvent cyclohexane/ethylacetate to afford 66 mg of product.

Yield= 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.35 (m, 5H), 1.55-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.65 (br, 1H), 3.65 (s, 3H), 4.77 (s, 2H), 7.53 (d, 2H), 7.67 (d, 2H).

MS (m/z) / M+1= 366/368

HPLC (uv putrity,λ= 214nm): 99.70%

The compounds of the following examples were prepared by the procedure described in example I20 using appropriate intermediates and reagents:

I20.1	[5-(4-Chloro-phenyl)-3-cyclopropylmethyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I20.2	3-[5-(4-Chloro-phenyl)-2-cyclohexylimino-

	[1,3,4]thiadiazol-3-yl]-propane-1,2-diol
I20.3	[5-(4-Chloro-phenyl)-3-(2-diethylamino-ethyl)-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Example I21: R1= cyclohexyl, R2= methyl, R3= 3- benzoic acid methyl ester

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole 7 (1.86 mmol, 590 mg) prepared by the procedure described in **example 7g** in anhydrous dioxane (20 mL), methyltrifluoromethane sulfonate (2.79 mmol, 316 µl) and triethylamine (2.23 mmol, 310 µl) were added. The mixture was stirred for 7h at RT. The mixture was filtered and the precipitate was then poured into diluted $NaHCO_3$ solution and washed with dichloromethane. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and concentrated under reduce pressure to give 200 mg of the title product.

Yield: 37%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 7.55 (t, 1H), 7.80 (d, 2H), 7.95 (d, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ= 214 nm): 99.9%

Example I21.1: R1= cyclohexyl, R2= methyl, R3= 3-benzoic acid

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

To a solution of compound I21 (30 mg, 0.09 mmol) in methanol (10 ml) and water (2.5 ml), K_2CO_3 (163 mg,1.17 mmol) was added. The mixture was heated at reflux for 3h, allowed to cool and concentrated in vacuo to give a crude material. This residue was poured into water and the suspension was carefully neutralised with a solution of HCl (0.1N) and the

aqueous phase was extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 10 mg of the title product.

Yield: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.55 (t, 1H), 7.80 (d, 1H), 7.95 (d, 1H), 8.15 (s, 1H), 13.3 (bs, 1H).

MS (m/z) / M+1= 318.3

HPLC (uv purity, λ= 214 nm): 99.6%

Example I21.2: R1= cyclohexyl, R2= methyl, R3= 3-benzamide 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in tetrahydrofuran (THF)/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue (150 mg, 0.32 mmol) in THF (2 ml) cooled to 10°C. After 3 hours at RT, the mixture was concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was purified by silica gel chromatography (eluted with dichloromethane/methanol at 99/1) to afford 14mg of the title product.

Yield: 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 4H), 2.65-2.75 (m, 1H), 3.60 (s, 3H), 7.52(s, 1H), 7.60 (dd, 1H), 7.85 (d, 1H), 7.98 (d, 1H), 8.15(s, 1H), 8.18(s, 1H).

MS (m/z) / M+1= 317

HPLC (uv purity, λ= 214 nm): 99.9%

Example I21.3: R1= cyclohexyl, R2= methyl, R3= 3-[N-(2-hydroxy-ethyl)]-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl).-N-(2-hydroxy-ethyl)-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (2ml) with triethylamine (90 μl, 0.64 mmol) was added at 0°C ethanolamine (20 μl, 0.32 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and extracted with ethyl acetate, washed with water and brine, dried with magnesium sulfate, filtred and reduce under pressure vacuum. The residue was purified by silica gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford 50 mg of the good product.

Yield: 43%

1H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.55-2.75 (m, 1H), 3.30-3.37 (m, 2H), 3.45-3.55 (m, 5H), 4.70 (t, 1H), 7.55(dd, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05(s, 1H), 8.60(t, 1H).

MS (m/z) / M+1= 361

HPLC (uv purity, λ= 214 nm): 99.7%

Example I21.4: R1= cyclohexyl, R2= methyl, R3= 3-(N-methyl)-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (4 ml) with triethylamine (90 µl, 0.64 mmol) was added at 0°C methylamine hydrochloride (44 mg, 0.64 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and basified with a solution of $NaHCO_3$, extracted with ethyl acetate; washed with water and brine, dried with magnesium sulfate, filtred and reduce under pressure vacuum. The residue was purified by silica gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford the desired product.

Yield: 9%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 2.82 (s, 3H), 3.55 (s, 3H), 7.60(t, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05(s, 1H), 8.55-8.65 (m, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm): 96.6%

Example I22: R1= cyclohexyl, R2= methyl, R3= 3,4-dihydroxyphenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzene-1,2-diol; compound with trifluoro methanesulfonic acid

Compound I22 was prepared from 1,3,4-thiadiazole 7g by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethanesulfonic acid salt.

Yield= 54.1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.53 (m, 5H), 1.64-1.69 (b, 1H), 1.78-1.84 (b, 1H), 2.03-2.10 (b, 2H), 3.19-3.27 (b, 1H), 3.84 (s, 3H), 6.90 (d, 1H), 7.13 (d, 1H), 7.20 (s, 1H), 9.55-9.63 (b, 1H), 9.75-9.81 (b, 1H), 9.96-10.3(b, 1H).

MS (m/z) / M+1= 306/307

HPLC (uv purity, λ= 214 nm)= 97.35 %

Example I23: R1= cyclohexyl, R2= methyl, R3= 3,5-dimethoxy-4-hydroxy-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-2,6-dimethoxy-phenol

Compound I23 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethansulfonic acid salt.

Yield= 13.9%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.12-1.27 (b, 1H), 1.27-1.41 (b, 2H), 1.41-1.54 (b, 2H), 1.63-1.70 (b, 1H), 1.80-1.87 (b, 2H), 2.03-2.11 (b, 2H), 3.17-3.26 (b, 1H), 3.88 (9H, s), 7.06 (s, 2H), 9.38-9.47 (b, 1H), 9.80-9.88 (b, 1H).

MS (m/z) / M+1= 350/351

HPLC (uv purity, λ= 214 nm)= 96.00%

Compounds I23.1 and I23.2 were prepared by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

I23.1	6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
I23.2	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol

Example I24: R1= cyclohexyl, R2= methyl, R3= 8-hydroxyquinolin-2-yl

2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-quinolin-8-ol

Compound I24 was prepared from the appropriate 1,3,4-thiadiazole **7** (procedure described in example 7d) by the procedure described in example I18.6. In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethansulfonic acid salt.

Yield =58.1%

^{1}H-NMR (400MHz, DMSO) δ ppm:1.25-1.36 (b, 1H), 1.45-1.67 (b, 4H), 1.74-1.81 (b, 1H), 1.90-1.96 (b, 2H), 2.18-2.22 (b, 2H), 3.40-3.50 (b, 1H), 4.02 (s, 3H), 7.35 (d, 1H), 7.63 (d, 1H), 7.69 (t, 1H), 8.21 (d, 1H), 8.64 (d, 1H), 10.08-10.13 (b, 1H), 10.21-10.28 (b, 1H).

MS (m/z) / M+1= 341/342

HPLC (uv purity, λ= 214 nm)= 94.88%

Example I25: R1= cyclohexyl, R2= methyl, R3= 2-pyrazyl

Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine

The 1,3,4-thiadiazole **7f** (0.770 mmol, 0.200 g) and methyltrifluoromethane sulfonate (0.924 mmol, 0.104 ml) were reacted in dioxane (7 ml). The residue, obtained after basification to pH 9-10 with a saturated solution of

carbonate of potassium, was subjected to silica gel chromatography, eluting with dichloromethane containing from 0 to 10% methanol to give the expected product.

Yield= 0.075g, 35.37%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.43 (b, 5H), 1.56-1.65 (b, 1H), 1.90-2.00 (b, 4H), 2.63-2.70 (b, 1H), 3.56 (s, 3H), 8.67 (s, 2H), 9.12 (s, 1H).

HPLC (uv purity, λ= 214 nm)= 98.32%

MS (m/z) / M+1= 276/277

Example I26: R1 =cyclohexyl, R2= methyl, R3= (E)-2-(3-hydroxy-4-methoxy-phenyl)-vinyl

5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol

Compounds I26 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents.The desired product was isolated by chromatography on silica gel eluting with dichloromethane containing from 0 to 7% methanol.

Yield= 0.025g, 24.1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.36 (b, 6H), 1.52-1.59 (b, 1H), 1.66-1.78 (b, 4H), 3.39 (s, 3H), 3.76 (s, 3H), 6.70-6.80 (b, 1H), 6.85-6.97 (b, 2H), 6.97-7.07 (b, 2H), 9.04 (s, 1H).

MS (m/z) / M+1= 346/347

HPLC (uv purity, λ= 214 nm)= 98.64%

Example I27: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-hydroxy-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol

Compounds I27 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents.The desired product was isolated by chromatography on silica gel (Alltech, 2g silice) eluting with cyclohexane

containing from 0 to 4% ethylacetate.

Yield= 0.015 g, 14.2%

^{1}H-NMR (400MHz, DMSO) δ ppm:1.01-1.20 (b, 5H), 1.39-1.44 (b, 1H), 1.53-1.63 (b, 4H), 2.4-2.48 (b, 1H), 3.30 (s, 3H), 3.65 (s, 3H), 6.64 (d, 1H), 6.87 (d, 1H), 7.00 (d, 1H), 9.38-9.43 (b, 1H).

MS (m/z) / M+1= 320/321

HPLC (uv purity, λ= 214 nm)= 99.08%

Example I28: R1= cyclohexyl, R2= methyl, R3= quinolin-8-yl
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compounds I28 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.

Yield: 41%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.70-2.80 (m, 1H),3.45 (s, 3H), 7.55-7.60 (m, 1H), 7.60-7.70 (m, 1H), 7.95-8.05 (m, 1H), 8.35-8.40 (m, 1H), 8.40-8.45 (m, 1H), 8.20-8.80 (m, 1H).

MS (m/z) / M+1= 325.3

HPLC (uv purity, λ= 214 nm): 99.9%

Example I29: R1= cyclohexyl, R2= methyl, R3= 4-dimethylamino-phenyl
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine

Compounds I29 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.The product was chromatographed on silica gel column using cyclohexane/ethyl acetate with a ratio 8/2 as solvent.

Yield: 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 6.70 (d, 2H), 7.40 (d, 2H).

MS (m/z) / M+1= 317.3

HPLC (uv purity, λ= 214 nm): 99.5%

Example I30: R1= cyclohexyl, R2= methyl, R3= 4-sulfonamide-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

Compounds I30 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.

Yield: 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 7.40 (s, 2H), 7.75 (d, 2H), 7.85 (d, 2H).

MS (m/z) / M+1= 353.2

HPLC (uv purity, λ= 214 nm): 98.5%

Example I31: R1= cyclohexyl, R2= methyl, R3= 5-chloroindol-2-yl

[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid

Compounds I31 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

(m, 1H), 1.75-1.85 (m, 2H),1.95-2.10 (m, 2H), 3.10-3.30 (m, 1H), 3.85 (bs, 3H), 7.10-7.15 (m, 1H), 7.15-7.20 (m, 1H), 7.40-7.50 (m, 1H), 7.75 (bs, 1H), 10 (bs, 1H), 12.40 (bs, 1H).

MS (m/z) / M+1= 347.3

HPLC (uv purity, λ= 214 nm): 95.2%

Compound I31.1 was prepared by the procedure described in example I31 using appropriate intermediates and reagents:

I31.1	2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Example I32: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4-methoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compounds I32 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was concentrated, filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 69%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 2H),1.90-2.05 (m, 2H), 3.05-3.20 (m, 1H), 3.8 (2s, 6H), 7.00 (d, 1H), 7.15-7.20 (m, 2H), 9.60 (bs, 1H), 9.75 (bs, 1H).

MS (m/z) / M+1= 320.3

HPLC (uv purity, λ= 214 nm): 98%

Example I33: R1= cyclohexyl, R2= methyl, R3= 4-hydroxy-phenyl 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compounds I33 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 95%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60 (m, 1H), 1.65 -1.75 (m, 2H),1.90-2.00 (m, 2H), 3.30-3.40 (m, 1H), 3.75 (s, 3H), 6.85 (d, 2H), 7.60 (d, 2H), 9.70 (bd, 1H), 10.25 (bd, 1H).

MS (m/z) / M+1= 290.3

HPLC (uv purity, λ= 214 nm): 95.6%

Example I34: R1= cyclohexyl, R2= methyl, R3= 3,4-dimethoxy-phenyl Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I34 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 20% ethylacetate.

Yield: 28%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.30 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.45-2.60 (m, 1H), 3.40 (s, 3H), 3.70 (2s, 6H), 6.95 (d, 1H), 7.05 (d, 1H), 7.10 (s, 1H)

MS (m/z) / M+1= 334.3

HPLC (uv purity, λ= 214 nm): 98.2%

Example I35: R1= cyclohexyl, R2= methyl, R3= 3-bromo-4-

methoxy-phenyl

[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I35 was prepared from 1,3,4-thiadiazole 7e, by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 15% ethylacetate.

Yield: 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.90 (s, 3H), 7.20 (d, 1H), 7.60 (d, 1H), 7.85 (s, 1H)

MS (m/z) / M+1= 384.2

HPLC (uv purity, λ= 214 nm): 95%

The compounds of the following examples were prepared by the procedure described in example I35 using appropriate intermediates and reagents:

I35.1	Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I35.2	Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Example I36: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-phenyl

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol

Compound I36 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C), using appropriate intermediates and reagents.

The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

Yield: 14%

^{1}H-NMR (400MHz , DMSO) δ ppm : 1.15-1.40 (m,5H), 1.55-1.65 (m,1H), 1.70-1.85 (m,4H), 2.55-2.65 (m,1H), 3.50 (s,3H), 6.85 (d,1H), 7.00-7.05 (m,2H), 7.25 (t,1H), 9.75 (s,1H)

MS (m/z) / M+1 =290.29

HPLC (uv purity, λ= 214 nm): 93.9%

Example I37: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid methyl ester

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

Compound I37 was prepared from the approriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents. The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

Yield: 47%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.65 (m, 1H), 3.50 (s, 3H), 3.80 (s, 3H), 7.70 (d, 2H), 8.00 (d, 2H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.1: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

To a solution of 1,3,4-thiadiazol I37 (80 mg,0.24 mmol) in methanol (10 ml) and water (2.5 ml), K_2CO_3 (434 mg,3.14 mmol) was added. The mixture was heated at 65°C during 3h then at RT over night. The solvent was removed by distillation under reduced pressure to give a crude material. This residue was poured into water, the suspension was carefully neutralised with a solution of HCl (0.1N) and the aqueous phase was extracted with dichloromethane. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 40 mg of the title product.

Yield: 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H),

7.75 (d, 2H), 8.00 (d, 2H), 13.15 (bs, 1H).
MS (m/z) / M+1= 318.4
HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.2: R1= cyclohexyl, R2= methyl, R3= 4-hydroxamic acid phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide

To a solution of LiOH monohydrate (37 mg, 0.75 mmol) in 0.8 ml of water, a solution of compound I37 (250 mg, 0.75 mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a solution of HCl (0.1N, 15 ml) was added. The resulting mixture was stirred for 20 min. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a solution of 75 mg (0.19 mmol) of this crude material in toluene (1 ml), a drop of pyridine, and thionylchloride (70 µl) were added and reacted at reflux during 4H. The volatiles were removed under reduced pressure. To a solution of this residue in anhydrous THF, O-(trimethylsilyl) hydroxylamine (230 µl, 0.47 mmol) was added with molecular sieves (3A) and the reaction mixture was stirred for 18H at RT. After filtration, the filtrate was concentrated under reduced pressure and the residue was treated with a 1 M solution of HCl, stirred at RT and then basified with a solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The title product was isolated by preparative HPLC on inverse phase (HYPERSYL C18) eluting with water containing from 5 to 95% acetonitrile during 20 mn.
Yield: 12 mg, 20%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.50 (s, 3H), 7.65 (d, 2H), 7.85 (d, 2H).
MS (m/z) / M+1= 333.2

HPLC (uv purity, λ= 214 nm): 94.9%

Example I37.3: R1= cyclohexyl, R2= methyl, R3= 4-benzamide 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of LiOH monohydrate (126 mg, 3.0 mmol) in 0.8 ml of water, a solution of I37 (1.0g, 3mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (8 ml) and a solution of HCl (0.1N, 60 ml) was added. The resulting mixture was stirred for 20 min. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of 120 mg (0.3 mmol) of this crude material in 2 ml of toluene, thionylchloride (2 ml) was added dropwise and the mixture was heated at reflux for 4H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue in THF (2 ml) cooled to 10°C. After allowing to stand 5 hours at RT, the mixture was concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was purified by silica gel chromatography (eluted with dichloromethane) to afford 64mg of the title product.

Yield: 67%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.45(bs, 1H), 7.75 (d, 2H), 7.95 (d, 2H), 8.05 (bs, 1H).

MS (m/z) / M+1= 317.35

HPLC (uv purity, λ= 214 nm): 99.3%

Example I37.4: R1= cyclohexyl, R2= methyl, R3= 4-N-(2H-tetrazol-5-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

To a solution of LiOH monohydrate (187 mg, 4.5 mmol) in 0.8 ml of water ,a solution of compound I37 (250 mg, 0.75 mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a 0.1 M solution of HCl was added to reach pH 6-7. After distillation of water, the crude material was dried over P_2O_5 in vacuo. Morpholine type resin (180 mg, 0.62 mmol) was added to a solution of 450 mg (0.62 mmol) of this crude material in 15ml of THF cooled to −15°C. Then isobutylchloroformate (105 µl; 0.8mmol) was added and the mixture was stirred at -15°C for 1H30 before addition of a suspension of amino-1H-tetrazole (80 mg, 0.74 mmol) in THF (10 ml). The reaction mixture was allowed to stand overnight at RT and the mixture was filtered over a silica gel. The filtrate was concentrated to dryness, and purified by preparative HPLC on inverse phase C18 (HYPERSYL), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford 10 mg of the title product. The compound was treated with a solution of ethanol/HCl to give the corresponding hydrochloride salt.

Yield: 4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-2.15 (m, 10H), 3.10-3.30 (m, 1H), 4.00 (bs, 3H), 8.10 (bd, 2H), 8.35 (bd, 2H), 12.70 (bs, 1H).

MS (m/z) / M+1= 385.46

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.5: R1= cyclohexyl, R2= methyl, R3= 4-(N-quinolin-8-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide

To a solution of LiOH monohydrate (794 mg, 19mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT

for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1mmol), N,Ndiisopropylethylamine (175 µl, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 10 mg of the title product.

Yield: 4.5%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.60-1.65 (m, 1H), 1.75-1.85 (m, 4H), 2.65-2.75 (m, 1H), 3.55 (s, 3H), 7.65-7.75 (m, 2H), 7.80 (d, 1H), 7.90 (d, 2H), 8.15 (d, 2H), 8.5 (d, 1H), 8.75 (d, 1H), 9.00 (d, 1H), 10.70 (s, 1H).

MS (m/z) / M+1= 444.13

HPLC (uv purity, λ = 214 nm): 96.4%

Example I37.6: R1= cyclohexyl, R2= methyl, R3= 4-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was

dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1 mmol), N,Ndiisopropylethylamine (260 µl, 1.5 mmol), 3-amino-2,6-dimethoxypyridine monohydrochloride (190 mg, 1mmol), molecular sieves (3A) and the reaction mixture was stirred 24h at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 10% ethyl acetate to afford 60 mg of the title product.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 6.35 (d, 1H), 7.70-7.80 (m, 3H), 8.00 (d, 2H), 9.65 (s, 1H).

MS (m/z) / M+1= 454

HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.7: R1= cyclohexyl, R2= methyl, R3= 4-N-isopropyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water , a solution of I37 (5.7g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (15 mg, 0.1mmol),

N,Ndiisopropylethylamine (175 µl, 1 mmol), isopropylamine (85 µl, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, Methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 40 mg of the title product.

Yield: 22%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 11H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 4.05-4.15 (m, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.30 (d, 1H).

MS (m/z) / M+1= 359

HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.8: R1= cyclohexyl, R2= methyl, R3= 4-N-ethyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide

To a solution of 2M ethylamine (1.8 ml, 3.6 mmol) in dichloroethane (5 ml) under nitrogen at 0°C, was added 2M trimethylaluminium (1.8 ml, 3.6 mmol) and the mixture was stirred at RT for 15min. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 48 h at RT. A solution of 2M ethylamine (0.8 ml, 1.6 mmol) and of 2M trimethylaluminium (0.8 ml, 1.6 mmol) were added to allow reaction to completion and the mixture was stirred at RT for another 24H. The mixture was diluted with 50 ml of dichloromethane and 30 ml of water, stirred for 2H, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford

60 mg of the title product.

Yield: 32%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20 (t, 3H), 1.20-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.80-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.35-3.45 (m, 2H), 3.65 (s, 3H), 7.90 (d, 2H), 8.05 (d, 2H), 8.65 (m, 1H).

MS (m/z) / M+1= 344.7

HPLC (uv purity, λ = 214 nm): 99.9%.

Example I37.8-1: R1= cyclohexyl, R2= methyl, R3= 4-(1-ethyl-1H-tetrazol-5-yl)-phenyl

Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine

To a solution of I37.8 (0.29 mmol, 100 mg) in acetonitrile (3 ml) at 0°C under a nitrogen atmosphere, sodium azide (0.44mmol, 28mg) and trifluoromethanesulfonic anhydre (0.44 mmol, 73 µl) were added. Then, the mixture was stirred overnight at room temperature and a satured solution of $NaHCO_3$ to pH=7 was added. The aqueous layer was extracted with dichloromethane and the organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of dicloromethane/methanol, then by HPLC (C_{18}-HYPERSYL column), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford the title product.

Yield: 9%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.47 (t, 3H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.50-2.55 (m, 1H), 3.55 (s, 3H), 4.52 (q, 2H), 7.85-7.90 (m, 4H).

MS (m/z) / M+1= 370

HPLC (uv purity, λ = 214 nm)= 96.8%

Example I37.9: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide

To a solution of N,N-dimethylethylenediamine (335 µl, 3 mmol) in dichloroethane (5 ml) under nitrogen atmosphere at 0°C, was added 2M trimethylaluminium (1.5 ml, 3 mmol), and the mixture was stirred at RT for 1H30. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 24 h at RT and 24h at 45°C. The mixture was diluted with 10ml of dichloromethane and 20ml of water, stirred for 1H30, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with a gradient of dichloromethane containing 0 to 5% methanol to afford 140 mg of the title product.

Yield: 60%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.25 (s, 6H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.75 (d, 2H), 7.90 (d, 2H), 8.50 (m, 1H)

MS (m/z) / M+1= 388

HPLC (uv purity, λ = 214 nm): 99.4%

Example I37.10: R1= cyclohexyl, R2= methyl, R3= 4-N-pyridin-4-ylmethyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water , a solution of compound I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of the crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (38 mg, 0.1mmol),

N,Ndiisopropylethylamine (175 µl, 1 mmol), 4-picolylamine (105 µl, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 3 days at RT. This mixture was filtered, and in the organic layer was added methylisocyanate resin (1 g, 1 mmol) and stirred 3 days at RT. After filtration, the filtrate was concentrated under reduced pressure. The solid was poured into water and the mixture was stirred for 1 h, before extraction with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% methanol to afford 30 mg of the title product.

Yield: 15%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.75 (m, 1H), 3.55 (s, 3H), 4.50 (d, 2H), 7.35 (d, 2H), 7.75 (d, 2H), 8.00 (d, 2H), 8.50 (d, 2H), 9.25 (m, 1H).

MS (m/z) / M+1= 408

HPLC (uv purity, λ = 214 nm): 99.7%

Example I37.11: R1= cyclohexyl, R2= methyl, R3= 4-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 µl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and 1-methyl-4-(methylamino)piperidine (0.6 mmol, 87 µl) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled under reduced pressure and the residue was poured into water before extraction with dichloromethane. The organic layer was washed with brine and then with a saturated solution of $NaHCO_3$, dried over magnesium sulfate, filtered and concentrated under vaccum. The residue was purified by

silica gel chromatography using a gradient of dichloromethane containing 0 to 15% methanol, to give the desired product.

Yield: 93.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.23-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.85 (m, 6H), 1.85-2.00 (m, 2H), 2.23-2.44 (m, 5H), 2.55-2.65 (m, 1H), 2.83 (s, 3H), 3.00-3.10 (m, 2H), 3.55 (s, 3H), 3.85-4.03 (m, 1H), 7.48 (dd, 2H), 7.70 (dd, 2H).

MS (m/z) / M+1= 428

HPLC (uv purity, λ = 214 nm)= 99.4%

Example I37.12: R1= cyclohexyl, R2= methyl, R3= 4-N-isobutyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 µl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and isobutylamine (2.3 mmol, 80 µl) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled and the residue was poured into water before extraction with dichloromethane. The organic layer was washed with brine, a saturated solution of $NaHCO_3$, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired product.

Yield: 86%

^{1}H-NMR (400MHz , DMSO) δ ppm: 0.90 (d, 6H), 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.72-1.90 (m, 5H), 2.60-2.70 (m, 1H), 3.10 (t, 2H), 3.55 (s, 3H), 7.72 (dd, 2H), 7.92 (dd, 2H), 8.55 (t, 1H).

MS (m/z) / M+1= 373

HPLC (uv purity, λ = 214 nm)= 98.4%

Example I37.13: R1= cyclohexyl, R2= methyl, R3: 4-N-methyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide

To a solution of I37.1 (4.25 mmol, 1,7 g) in DMF (20,5 ml) was added N-ethyldiisopropylamine-N,N-diisopropylethylamine (13.6 mmol, 1.615 ml), benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (5.1 mmol, 2.265 g), 1-hydroxy-7-azabenzotriazole (2.125 mmol, 290 mg) and a solution of methylamine at [2N] in methanol (5.1 mmol, 3.55 ml). The mixture was stirred at room temperature overnight. The mixture was reduced under pressure vacuum, extracted with dichloromethane in water. The organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 4% methanol, to give a residue which was stirred in diethylether during one hour. The precipitate was filtred and dried under vacuum over P_2O_5 to give 550 mg of the desired product.

Yield: 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.45 (m, 5H), 1.55-1.68 (m, 1H), 1.68-1.83 (m, 4H), 2.60-2.70 (m, 1H), 2.80 (d, 3H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H), 8.55 (q, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I37.13-1: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

To a suspension of I37.13 (0.3 mmol, 100 mg) in dimethylformamide (1 ml), sodium hydride at 60% dispersion in mineral oil (0.6 mmol, 24 mg), 2-dimethylaminoethylchloride hydrochloride (0.36 mmol, 52 mg) and K_2CO_3 (0.36 mmol, 50 mg) were added. The mixture was stirred overnight at 40°C. Then, potassium ter-butoxyde (0.18 mmol, 20 mg) was added and the mixture was stirred during 24H. 2-dimethylaminoethylchloride hydrochloride (0.18 mmol, 26 mg), and K_2CO_3 (0.18 mmol, 25 mg) were added and

warmed at 40°C overnight. The mixture was reduce under pressure vacuum to give a residue which was purified by silica gel chromatography, eluting with a gradient of dicloromethane containing from 0 to 6% methanol to afford the title product.

Yield: 16%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.00 (s, 3H), 2.25 (s, 3H), 2.30-2.40 (m, 1H), 2.60-2.70 (m, 1H), 2.88-3.02 (m, 3H), 3.55 (s, 3H), 7.45 (dd, 2H), 7.70 (dd, 2H).

MS (m/z) / M+1= 402

HPLC (uv purity, λ = 214 nm)= 98.8%

Example I37.14: R1= cyclohexyl, R2= methyl, R3= 4-(3-hydroxy-methyl-piperidin-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone

Compound I37.14 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, to give the desired product.

Yield: 34%

^{1}H-NMR (350K, 400MHz, DMSO) δ ppm: 1.20-1.50 (m, 7H), 1.50-1.70 (m, 3H), 1.70-1.85 (m, 5H), 2.63-2.78 (m, 2H), 2.88-2.98 (m, 1H), 3.18-3.28 (m, 1H), 3.28-3.38 (m, 1H), 3.50 (s, 3H), 3.75-4.10 (m, 2H), 4.18-4.28 (m, 1H), 7.45 (dd, 2H), 7.68 (dd, 2H).

MS (m/z) / M+1= 415

HPLC (uv purity, λ= 214 nm)= 95.4%

Example I37.15: R1= cyclohexyl, R2= methyl, R3= 4-{N-[(S)-1-tert-butoxycarbonyl-2-(4-hydroxy-phenyl)-ethyl]}benzamide

2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester

Compound I37.15 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol and then the product was washed with water, extracted with ethylacetate and the organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum to give the title product.

Yield: 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 14H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 4H), 2.58-2.68 (m, 1H), 2.91-3.01 (m, 2H), 3.52 (s, 3H), 4.45-4.51 (m, 1H), 6.65 (dd, 2H), 7.08 (dd, 2H), 7.71 (dd, 2H), 7.90 (dd, 2H), 8.75 (d, 1H), 9.15 (s, 1H).

MS (m/z) / M+1= 537

HPLC (uv purity, λ= 214 nm)= 96.3%

Example I37.15-a: R1= cyclohexyl, R2= methyl, R3= 4-[N-((S)-1-carboxy-2-(4-hydroxy-phenyl)-ethyl)]benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid

To a solution of I37.15 (0.186 mmol, 100 mg) in dichloromethane (1.5 ml), trifluoroacetic acid (4.4 mmol, 378 µl) was added and the mixture was stirred at reflux during 2 hours. The mixture was purified by silica gel chromatography, eluting with a gradient of diclorornethane containing from 0 to 10% methanol to afford 60 mg of the title product.

Yield: 54%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.12-1.52 (m, 5H), 1.58-1.68 (m, 1H), 1.73-1.85 (m, 2H), 1.85-2.05 (m, 2H), 2.88-3.11 (m, 3H), 3.75 (s, 3H), 4.48-4.60 (m, 1H), 6.62 (dd, 2H), 7.08 (dd, 2H), 7.85 (dd, 2H), 7.95 (dd, 2H), 9.15 (s, 1H), 12.75 (s, 1H).

MS (m/z) / M+1= 481

HPLC (uv purity, λ= 214 nm)= 98%

Example I37.16: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-tert-butoxycarbonyl)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester

Compound I37.16 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol, and the product was washed with water, filtrered and dried under pressure vacuum with P_2O_5 to give the title compound.

Yield: 65%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 17H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.58-2.68 (m, 1H), 3.52 (s, 3H), 4.35 (q, 1H), 7.73 (dd, 2H), 7.95 (dd, 2H), 8.75 (d, 1H).

MS (m/z) / M+1= 445

HPLC (uv purity, λ= 214 nm)= 99.3%

Example I37.16-a: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-carboxy)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid

To a solution of I37.16 (0.225 mmol, 100 mg) in dichloromethane (1 ml) at 0°C, trifluoroacetic acid (5.85 mmol, 457 μl) was added and the mixture was stirred at room temperature overnight. The mixture was purified by silica gel chromatography, eluting with a gradient of diclorومethane containing from 0 to 5% methanol to afford 40 mg of the title product.

Yield: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.48 (m, 8H), 1.55-1.65 (m, 1H), 1.70-1.81 (m, 2H), 1.81-2.00 (m, 2H), 2.89-3.05 (m, 1H), 3.71 (s,3H), 4.44 (q, 1H), 7.87 (dd, 2H), 8.03 (dd, 2H), 8.82 (d, 1H), 12.57 (s, 1H).

MS (m/z) / M+1= 388/389

HPLC (uv purity, λ= 214 nm)= 97.9%

Example I37.17: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyridin-2-yl-piperazine-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone

Compound I37.17 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtered and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.48 (m, 5H), 1.55-1.65 (m, 1H), 1.70-2.00 (m, 4H), 2.62-2.92 (m, 1H), 3.35-3.87 (m, 11H), 6.67 (dd, 1H), 6.88 (d, 1H), 7.45-7.63 (m, 3H), 7.78 (dd, 2H), 8.12 (d, 1H).

MS (m/z) / M+1= 463

HPLC (uv purity, λ = 214 nm)= 99.9%

Example I37.18: R1= cyclohexyl, R2= methyl, R3= 4-[4-(4-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone

Compound I37.18 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 31%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.65-1.86 (m, 4H), 2.56-2.70 (m, 1H), 2.96-3.10 (m,

4H), 3.37-3.85 (m, 7H), 6.67 (dd, 1H), 6.92-7.12 (m, 4H), 7.51 (dd, 2H), 7.71 (dd, 2H).

MS (m/z) / M+1= 480

HPLC (uv purity, λ= 214 nm)= 98.6%

Example I37.19: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3,4,5-trimethoxy-benzyl)]-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide

Compound I37.19 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of cyclohexane containing 0 to 30% ethylacetate, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.19-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.71-1.88 (m, 4H), 2.60-2.70 (m, 1H), 3.50-3.55 (m, 3H), 3.55 (s, 3H), 3.75 (s, 6H), 4.42 (d, 2H), 6.65 (s, 4H), 7.70-7.80 (m, 1H), 8.00 (d, 1H), 9.10 (t, 1H).

MS (m/z) / M+1= 497

HPLC (uv purity, λ= 214 nm)= 99.5%

Example I37.20: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyrimidin-2-yl-piperazin-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone

Compound I37.20 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 1% methanol, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.41 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.75 (m, 4H), 2.55-2.70 (m, 1H), 3.00-3.90 (m, 11H), 6.65 (t, 1H), 6.88 (d, 1H), 7.50 (dd, 2H), 7.70 (dd, 2H), 8.38 (d, 2H).
MS (m/z) / M+1= 464
HPLC (uv purity, λ= 214 nm)= 97%

Example I37.21: R1= cyclohexyl, R2= methyl, R3= 4-(4-methyl-piperazine-1-carbonyl)-phenyl
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone
Compound I37.21 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.
The residue was purified by silica gel chromatography using a gradient of of dichloromethane containing 0 to 10% methanol, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.
Yield: 55%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.69-1.81 (m, 4H), 2.25 (s, 3H), 2.33-2.52 (m, 4H), 2.59-2.69 (m, 1H), 3.25-3.45 (m, 2H), 3.52 (s, 3H), 3.55-3.70 (m, 2H), 7.78 (dd, 2H), 7.71 (dd, 2H).
MS (m/z) / M+1= 400
HPLC (uv purity, λ= 214 nm)= 99.6%

Example I37.22: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3-(4-methyl-piperazin-1-yl)-propyl)]benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide
Compound I37.22 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.
The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 10% methanol, to give a product which was stirred in diethylether, filtred and dried under reduced pressure over P_2O_5 to give the

desired product.

Yield: 3.5%

^{1}H-NMR (400MHz, $CDCl^3$): δ ppm: 1.20-1.50 (m, 5H), 1.60-2.05 (m, 7H), 2.35 (s, 3H), 2.48-2.85 (m, 11H), 3.52-3.64 (m, 2H), 3.50 (s, 3H), 7.68 (dd, 2H), 7.87 (dd, 2H), 8.00-8.08 (m, 1H).

MS (m/z) / M+1= 457

HPLC (uv purity, λ= 214 nm)= 97.2%

Example I37.23: R1= cyclohexyl, R2= methyl, R3= 4-N-[(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

To a solution of 2-(aminomethyl)-1-ethylpyrrolidine (7.5 mmol, 967 mg) in dichloroethane (10 ml) under nitrogen atmosphere, was added dropwise trimethylaluminium [2N] in toluene (7.5 mmol, 3.8 ml) and the mixture was stirred at room temperature during 2 hours. A solution of compound I37 (1.5 mmol, 500 mg) in dichloroethane (10 ml) was then added and the stirring was pursued at 65°C overnight. At room temperature, dichloromethane (30 ml) and water (50 ml) were added and the mixture was stirred several hours. The mixture was filtered through celite, extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 10% methanol to afford the desired product.

Yield: 79%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05 (t, 3H), 1.20-1.42 (m, 5H), 1.55-1.70 (m, 4H), 1.70-1.85 (m, 5H), 2.10-2.18 (m, 1H), 2.25-2.35 (m, 1H), 2.55-2.70 (m, 2H), 2.80-2.90 (m, 1H), 3.00-3.12 (m, 2H), 3.39-3.49 (m, 1H), 3.55 (s, 3H), 7.71 (dd, 2H), 7.92 (dd, 2H), 8.49 (t, 1H).

MS (m/z) / M+1= 428

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I37.24: R1= cyclohexyl, R2= methyl, R3= 4-N-[(pyridin-3-ylmethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide

Compound I37.24 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 2-(aminoethyl)pyridine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 8% methanol to afford the desired product.

Yield: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 4.50 (d, 2H), 7.35-7.40 (m, 1H), 7.70-7.80 (m, 3H), 8.00 (dd, 2H), 8.45-8.50 (m, 1H), 8.57 (s, 1H), 9.30 (t, 1H).

MS (m/z) / M+1= 408

HPLC (uv purity, λ= 214 nm)= 98.6%

Example I37.25: R1= cyclohexyl, R2= methyl, R3= 4-(N-benzyl)-benzamide

N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

Compound I37.25 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and benzylamine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 2% methanol to afford the desired product.

Yield: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.65-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.52 (s, 3H), 4.48 (d, 2H), 7.19-7.39 (m, 5H), 7.72 (dd, 2H), 7.98 (dd, 2H), 9.13 (t, 1H)

MS (m/z) / M+1= 407

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I37.26: R1= cyclohexyl, R2= methyl, R3= 4-[N-(1-

benzyl-piperidin-4-yl)]-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

Compound I37.26 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 4-amino-1-benzylpiperidine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 8% methanol to afford the desired product.

Yield: 50%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.53-1.65 (m, 3H), 1.70-1.83 (m, 6H), 1.97-2.07 (m, 2H), 2.70-2.80 (m, 1H), 2.77-2.87 (m, 2H), 3.47 (s, 2H), 3.55 (s, 3H), 3.70-3.85 (m, 1H), 7.22-7.35 (m, 5H), 7.70 (dd, 2H), 7.93 (dd, 2H), 8.35 (d, 1H).

MS (m/z) / M+1= 490

HPLC (uv purity, λ= 214 nm)= 96.4%

Example I37.27: R1= cyclohexyl, R2= methyl, R3= 4-[N-(2-ethyl-2H-pyrazol-3-yl)]-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide

Compound I37.27 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 5-amino-1-ethylpyrazole).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 8H), 1.60-1.70 (m, 1H), 1.75-1.87 (m, 4H), 2.63-2.73 (m, 1H), 3.55 (s, 3H), 4.05 (q, 2H), 6.25 (d, 1H), 7.45 (d, 1H), 7.83 (dd, 2H), 8.10 (dd, 2H), 10.40 (s, 1H).

MS (m/z) / M+1= 411

HPLC (uv purity, λ= 214 nm)= 99.7%

Example I37.28: R1= cyclohexyl, R2= methyl, R3= 4-(2-morpholin-4-yl-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide

Compound I37.28 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and N-(2-aminoethyl)morpholine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.

Yield: 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.63 (m, 1H), 1.70-1.83 (m, 5H), 2.35-2.50 (m, 6H), 2.57-2.67 (m, 1H), 3.38 (q, 2H), 3.50 (s, 3H), 3.52-3.57 (m, 4H), 7.80 (dd, 2H), 7.90 (dd, 2H), 8.50 (t, 1H)

MS (m/z) / M+1= 430

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I37.28-1: R1= cyclohexyl, R2= methyl, R3= 4-[(N-cyano-N'-ethylmorpholine)-carboxyimidamine]-phenyl

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of I37.28 (2.33 mmol, 1 g) in toluene (15 ml), Lawesson's reagent (4.65 mmol, 1.88 g) was added and the mixture was stirred overnight at reflux. After cooling at room temperature, the mixture was acidified with a solution of HCl at 5% (3.5 ml) then basified with a solution of $NaHCO_3$. The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N(2-morpholin-4-yl-ethyl)thiobenzamide.

Yield: 56%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.60-2.75 (m, 3H), 3.52 (s, 3H), 3.55-3.63 (m, 4H), 3.78 (t, 2H), 3.80-3.90 (m, 2H), 7.70 (dd, 2H), 7.82 (dd, 2H), 10.28 (t, 1H).

To a solution of 4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N(2-morpholin-4-yl-ethyl)thiobenzamide (1.12 mmol, 500 mg) in THF (20 ml), sodium hydride (60% dispersion in mineral oil, 1.12 mmol, 44 mg) was added and the mixture was warmed at reflux during one hour. After cooling at room temperature, methyl iodide (1.35 mmol, 84 μl) was added and the mixture was warmed 4 hours at reflux and then overnight at room temperature. The mixture was concentrated under reduced pressure to give a crude material which was solubilized in ethanol (50 ml). To this solution, cyanamide(1.8 mmol, 75 mg) and triethylamine (0.9 mmol, 125μl) were added and the mixture was stirred 2 days at reflux. Mercury(II)chloride (1.68 mmol, 457 mg) and cyanamide (2.35 mmol, 100 mg) were added and the reaction was allowed to stir 3 days at room temperature. The mixture was concentrated under reduced pressure and the residue was diluted in ethyl acetate and filtered through celite. The filtrate was concentrated under vacuum. The residue was chromatographed on silica gel using a gradient of dichloromethane containing from 0 to 5% methanol to afford the title compound.

Yield: 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.40-2.50(m, 4H), 2.50-2.60(m, 2H), 2.60-2.70 (m, 1H), 3.45-3.55(m, 2H), 3.55 (s, 3H), 3.55-3.65(m, 4H), 7.68 (dd, 2H), 7.52 (dd, 2H), 9.15 (t, 1H).

MS (m/z) / M+1= 454

HPLC (uv purity, λ= 214 nm) = 95%

Example I37.29: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

Compound I37.29 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 1-(2-aminoethyl)pyrolidine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 14% methanol to afford the desired product.

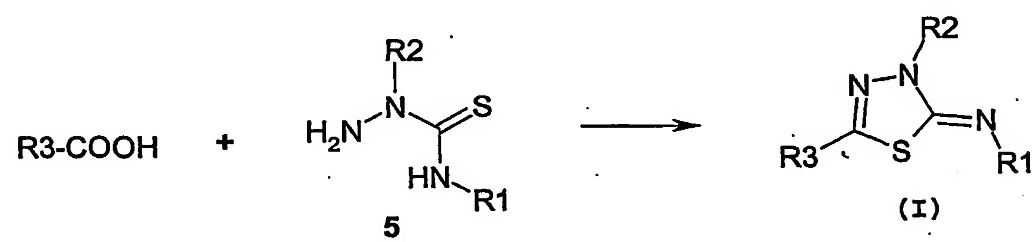
Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.87 (m, 9H), 2.45-2.70 (m, 7H), 3.35-3.45 (m, 2H), 3.60 (s, 3H), 7.73 (dd, 2H), 7.95 (dd, 2H), 8.55 (t, 1H).

MS (m/z) / M+1= 414

HPLC (uv purity, λ= 214 nm)= 99.9%

Protocol D :



EXAMPLE I: PROTOCOL D

Example I15: R1= cyclohexyl, R2= methyl, R3= 4-methylsulfonyl-phenyl

Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

To a mixture of 4-methylsulfonyl-benzoic acid (2.5 mmol, 500 mg), 2-methylthiosemicarbazide 5a (2.5 mmol, 468 mg) in anhydrous dioxane (5 mL) at 65°C, $POCl_3$ (3 mmol, 280 μl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The aqueous phase was

extracted with dichoromethane. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate finishing with the ratio 80/20) to afford 230 mg of the title compound.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.45 (m, 5H), 1.65-1.75 (m, 1H), 1.75-1.95 (m, 4H), 1.70-1.80 (m, 1H), 3.35 (s, 3H), 3.65(s, 3H), 8.05(dd, 4H).

MS (m/z) / M+1= 352.5

HPLC (uv purity, λ= 214 nm): 95.3%

The compounds of the following examples were prepared by the procedure described in example I15 using appropriate intermediates and reagents:

I15.1	[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
I15.2	Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Example I38: R1= cyclohexyl, R2= Me, R3= 3-pyridyl

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compound I38 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 10% ethylacetate.

Yield= 0.06 g, 13.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.44 (m, 5H), 1.59-1.64 (b, 1H), 1.73-1.83 (b, 4H), 2.61-2.70 (b, 1H), 3.54 (s, 3H), 7.50-7.53 (m, 1H), 8.04 (d, 1H), 8.63-8.67 (m, 1H), 8.85 (s, 1H).

MS (m/z) / M+1= 275/276

HPLC (uv purity, λ= 214 nm)= 95.87%

Example I39: R1= cyclohexyl, R2= methyl, R3= 3-sulfamoyl-phenyl

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

Compound I39 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with dichloromethane containing from 0 to 5% methanol.

Yield= 8.0 %

^{1}H-NMR (400MHz, DMSO) δppm: 1.18-1.41 (m, 5H), 1.58-1.63 (m, 1H), 1.73-1.84 (m, 4H), 2.60-2.67 (m, 1H), 3.56 (s, 3H), 7.48 (s, 2H), 7.67 (t, 1H), 7.82-7.90 (m, 2H), 8.12 (s, 1H).

MS (m/z) / M+1= 353/354

HPLC (uv purity, λ= 214 nm)= 97.55%

Example I40: R1= cyclohexyl, R2= methyl, R3= benzo[1,3]dioxol-5-yl

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine

Compound I40 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 15% ethylacetate.

Yield: 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.70 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.50 (s, 3H), 6.15 (s, 2H), 7.00 (d, 1H), 7.15 (d, 1H), 7.25 (s, 1H)

MS (m/z) / M+1= 318

HPLC (uv purity, λ= 214 nm): 99.9%

Example I41: R1= cyclohexyl, R2= methyl, R3= 3,4,5-trimethoxyphenyl

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I41 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with heptane containing from 0 to 20% diethylether.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.50 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.65-2.70 (m, 1H), 3.50 (s, 3H), 3.70 (s, 3H), 3.85 (s, 6H), 6.90 (s, 2H)

MS (m/z) / M+1= 364.49

HPLC (uv purity, λ= 214 nm): 99.9%

EXAMPLE I: PROTOCOL A

Example I42 : R1= cyclopentyl, R2= methyl, R3= 4-cyano-phenyl

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

To a suspension of 1,3,4-thiadiazolium perchlorate (3c) (0.86 mmol, 300 mg) in ethanol (20 ml), cyclopentylamine (1.03 mmol, 102 μl) and triethylamine (1.03 mmol, 264 μl) were added, and the mixture was stirred at reflux overnight. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with water and a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane starting with a ratio 0/100 to 20/80) to isolate 210 mg of the pure product.

Yield= 85.7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.95 (m, 8H), 3.15-3.25 (m, 1H), 3.50 (s, 3H), 7.80 (dd, 2H), 7.92 (dd, 2H).
MS (m/z) / M+1= 285

Example I43: R1= cycloheptyl, R2 = methyl, R3= 4-cyanophenyl
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

The compound I43 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 70.6%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.85 (m, 12H), 2.75-2.85 (m, 1H), 3.50 (s, 3H), 7.80 (dd, 2H), 7.90 (dd, 2H).
MS (m/z) / M+1= 313

Example I44: R1= 4-fluorophenyl, R2= Methyl, R3= 4-cyano-phenyl
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I44 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 71.1%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.03-7.10 (m, 2H), 7.16-7.25 (m, 2H), 7.83 (dd, 2H), 7.93 (dd,2H).
MS (m/z) / M+1= 311

Example I45: R1= 3-phenol, R2= methyl, R3= 4-cyano-phenyl
4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I45 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on

silica gel eluting with a gradient of dichloromethane containing from 0 to 20% methanol.

Yield = 99%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.70 (s, 3H), 6.41-6.55 (m, 3H), 7.15 (t, 1H), 7.82 (dd, 2H), 7.91 (dd,2H), 9.42 (s, 1H).

MS (m/z) / M+1= 309

Example I46: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-cyano-phenyl

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

The compound I46 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). In this particular case, the residue was precipitated in ethylacetate to afford the pure product.

Yield= 65.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.74 (s, 3H), 7.24-7.37 (m, 3H), 7.44-7.51 (m, 1H), 7.85 (dd, 2H), 7.94 (dd,2H), 13.31 (b, 1H).

MS (m/z) / M+1= 355

Example I47: R1= 4-methyl-cyclohexyl, R2= methyl, R3= 4-cyano-phenyl

I47a : 4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I47b : 4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I47 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate to give the cis and trans isomers.

Yield= 68.6%

Compound cis: I47a

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.92 (d, 3H), 1.38-1.68 (m, 9H), 2.85-2.92 (m, 1H), 3.55 (s, 3H), 7.80 (dd, 2H), 7.92 (dd, 2H).

MS (m/z) / M+1= 313

Compound trans:I47b

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.88 (d, 3H), 0.94-1.09 (m, 2H), 1.30-1.45 (m, 3H), 1.64-1.83 (m, 4H), 2.48-2.60 (m, 1H), 3.52 (s, 3H), 7.80 (dd, 2H), 7.92 (dd, 2H).

MS (m/z) / M+1= 313

Example I48: R1= trans-4-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I48 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). Using 0.86 mmol of thiadiazolium, an excess of trans-4-aminocyclohexanol hydrochloride (7.7 mmol) and 8.6 mmol of triethylamine. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.

Yield= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.42 (m,4H), 1.73-1.89 (m,4H), 2.52-2.62 (m,1H), 3.40-3.50(m,1H), 3.53 (s, 3H), 4.50 (s, 1H), 7.80 (dd, 2H), 7.92 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I49: R1= exo-2-norbornyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I49 was prepared by the procedure described in example I48 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 8% ethylacetate.

Yield= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.20 (m, 3H), 1.26-1.35 (m, 1H), 1.40-1.53 (m, 2H), 1.56-1.61 (m, 1H), 1.70-1.79 (m, 1H), 2.09-2.14 (m, 1H), 2.24-2.29 (m, 1H), 2.71-2.78 (m, 1H), 3.52 (s, 3H), 7.80 (dd, 2H), 7.91 (dd, 2H).

MS (m/z) / M+1= 311

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I50: R1= (1R*, 2R*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I50 was prepared by the procedure described in example I48 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% ethylacetate.

Yield= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.58-1.75 (m, 3H), 1.80-1.90 (m, 1H), 2.38-2.49 (m, 1H), 3.30-3.40 (m, 1H), 3.55 (s, 3H), 4.50 (s, 1H), 7.80 (dd, 2H), 7.92 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I51: R1= (1R*, 2S*)-2-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Compound I51 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). 1,3,4-thiadiazolium perchlorate (0.287 mmol, 100 mg) in ethanol (6 ml), cis-2-aminocyclohexanol hydrocloride (2.58 mmol, 390 mg) and triethylamine (2.87 mmol, 400 μl) were added. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.

Yield= 72%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.80 (m, 8H), 2.83-2.97 (m, 1H), 3.52-3.70 (m, 4H), 4.10-4.20 (m, 1H), 7.80 (dd, 2H), 7.94 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (uv purity, λ = 214 nm)= 98.7%

Examples I52-a and I52-b : R1= 3-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

I52-a: 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I52-b: 4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compounds I52-a and I52-b were prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). A mixture of 1,3,4-thiadiazolium perchlorate (3c) (3.5 mmol, 1.22 g) in ethanol (80 ml), racemic-3-aminocyclohexanol (4.2 mmol, 485 mg) and triethylamine (4.2 mmol, 587 μl) was stirred at reflux during 4H. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 60% ethylacetate to give 120 mg of the trans isomer and 260 mg cis isomer.

1R*, 3R* isomer (I52a)

Yield = 11%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.35-1.50 (m, 2H), 1.50-1.70 (m, 6H), 3.04-3.12 (m, 1H), 3.54 (s, 3H), 3.88-3.96 (m, 1H), 4.44 (d, 1H), 7.80 (dd, 2H), 7.94 (dd, 2H).

1R*, 3S* isomer (I52b)

^{1}H (400MHz, DMSO) δ ppm: 1.03-1.30 (m, 4H), 1.64-1.78 (m, 2H), 1.78-1.87 (m, 1H), 1.98-2.04 (m, 1H), 2.58-2.70 (m, 1H), 3.40-3.58 (m, 4H), 4.61 (s, 1H), 7.44 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.07 (s, 1H).

Example I53: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(methylsulfonyl)phenyl

(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I53 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). A mixture of 1,3,4-thiadiazolium perchlorate (3b) (1 mmol, 400 mg), ethanol (25 ml), 3-aminocyclohexanol (1.2 mmol, 140 mg) and triethylamine (2.5 mmol, 350 μl) was stirred at reflux during 3H. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% ethylacetate. The product was then purified by HPLC on Kromasil C18 column with a gradient of acetonitrile/water 95/5 to 5/95 to give the pure product.

Yield= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.30-1.69 (m, 8H), 3.00-3.10 (m, 1H), 3.21 (s, 3H), 3.52 (s, 3H), 3.82-3.95 (m, 1H), 4.35 (d, 1H), 7.85 (dd, 2H), 7.98 (dd, 2H)

MS (m/z) / M+1= 367/369

HPLC (uv purity, λ= 214 nm)= 98.9%

Example I54: R1= (1R*, 3R*)-3-Hydroxy-cyclohexyl, R2= methyl, R3= 4-benzoic acid

4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

To a solution of I52a (3.18 mmol, 1 g) in isopropanol (20ml), a solution of KOH [6N] (15.9 mmol, 2.6 ml) was added and the mixture was stirred at reflux during 4 days. The mixture was acidified to pH= 6-7 with a solution of HCl and concentrated under reduced pressure to give the carboxylic acid derivative I54.

1H (400MHz, DMSO) δ ppm : 1.32-1.70(m, 8H), 3.03-3.12 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.35-4.50 (m, 1H), 7.75 (dd, 2H), 8.00 (dd,2H), 13.15 (s, 1H)

Example I55: R1= (1R*, 3R*)-3-hydroxycyclohexyl, R2= methyl, R3= 4-[N-(2-morpholin-4-yl-ethyl)]benzamide

4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide

Compound I55 was prepared by the procedure described in exemple I37.11 using I54 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 4% methanol, to give the desired product.

Yield: 14%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.35-1.70 (m, 8H), 2.35-2.52 (m, 6H), 3.02-3.12 (m, 1H), 3.32-3.45 (m, 2H), 3.50-3.62 (m, 7H), 3.88-3.95 (m, 1H), 4.40 (d, 1H) 7.72 (dd, 2H), 7.92 (dd, 2H), 8.50 (s, 1H).

MS (m/z) / M+1= 446

HPLC (uv purity, λ= 214 nm)= 96.6%

Example I56: R1= trans-4-hydroxycyclohexyl, R2 = methyl, R3= 4-benzoic acid

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

To a solution of I48 (1.9 mmol, 600 mg) in ethanol (15 ml) and isopropanol (15 ml),a solution of KOH [6N] (5.7 mmol, 960 µl) was added and stirred at reflux during 7H. The mixture was acidified to pH = 6-7 with a solution of HCl and then concentrated under reduced to give the carboxylic acid derivative I56.

^{1}H-RMN (400MHz, DMSO) δ ppm: 1.22-1.32 (m, 2H), 1.60-1.80 (b, 2H), 1.90-2.04 (m, 4H), 3.41-3.50 (m, 1H), 4.00 (s, 3H), 7.80-7.90 (m, 2H), 8.00-8.10 (m, 2H), 11.00 (s, 1H).

Example I57: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-2-hydroxy-1,1-dimethyl-ethyl)benzamide

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

Compound I57 was prepared by the procedure described in exemple I37.11 using I56 as a starting material.The residue

was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 9% methanol, to give the expected product.

Yield: 20%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.15-1.45 (m, 10H), 1.70-1.90 (m, 4H), 2.50-2.60 (m, 1H), 3.40-3.55 (m, 6H), 4.50 (d, 1H) 4.85 (d, 1H), 7.60 (s, 1H), 7.70 (dd, 2H), 7.89 (dd, 2H).

MS (m/z) / M+1= 405

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I58: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-2-hydroxy-1,1-dimethyl-ethyl)benzamide

4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

Compound I58 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and 1,1-dimethyl-2-ethanolamine).

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, to give the desired product.

Yield: 58%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.20-1.70 (m, 14H), 3.02-3.12 (m, 1H), 3.40-3.60 (m, 5H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 4.85 (d, 1H), 7.60 (s, 1H), 7.68 (dd, 2H), 7.85 (dd, 2H)

MS (m/z) / M+1= 405

HPLC (uv purity, λ= 214 nm)= 94.4%

Example I59: (1R*, 3R*)-3-hydroxycyclohexyl, R2= methyl, R3= 4-(N-tert-butyl)-benzamide

N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I59 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and isobutylamine). The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 10%.

Yield: 33%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 17H), 3.02-3.12 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.68 (dd, 2H), 7.80-7.90 (m, 3H).

MS (m/z) / M+1= 389

HPLC (uv purity, λ= 214 nm)= 94.1%

Example I60: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-[N-(1,1-dimethyl-3-oxo-butyl)]-benzamide N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of diacetoamine hydrogenoxalate (3 mmol, 616 mg) in DMF (6 ml) under nitrogen atmosphere, morpholine resin [3.47 mmol/g] (7 mmol, 2 g) was added, and the mixture was stirred at room temperature during 30 minutes and then filtered. A mixture of acid I54 (0.6 mmol), the filtrate, N,N-diisopropylethylamine(1.32 mmol, 227 μl), benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (0.72 mmol, 318 mg), 1-hydroxy-7-azabenzotriazole (0.3 mmol, 82 mg) was stirred at room temperature during 4H. The mixture was concentrated and then diluted in dichloromethane. The organic layer was washed with a satured solution of ammonium chloride, a satured solution of $NaHCO_3$, with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 8% methanol. The compound was purified by HPLC (Kromasil C18 column) eluting with acetonitrile/water 95/5 to 5/95 to give the desired product.

Yield: 10%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 14H), 2.05 (s, 3H), 2.92-3.10 (m, 3H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.68 (dd, 2H), 7.85 (dd, 2H), 7.95 (s, 1H).

MS (m/z) / M+1= 431

HPLC (uv purity, λ= 214 nm)= 99.3%

Example I61: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-[N-(2-cyano-1,2,2-trimethyl-ethyl)]-benzamide
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I61 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and 2-amino-2,3-dimethylbutanenitrile).

The residue was purified by silica gel chromatography using a gradient of cyclohexane containing 0 to 70% ethylacetate, to give the title product.

Yield: 8%

^{1}H-NMR (400MHz, DMSO): δ ppm: 0.95 (d, 3H), 1.10 (d, 3H), 1.30-1.70 (m, 11H), 2.45-2.65 (m, 1H), 3.00-3.10 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.70 (dd, 2H), 7.90 (d, 2H), 8.65 (s, 1H).

MS (m/z) / M+1= 428

HPLC (uv purity, λ= 214 nm)= 99.4%

Example I62: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-1-methoxycarbonyl-cyclopropyl)-benzamide
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester

Compound I62 was prepared by the procedure described in example I37.24 using appropriate intermediates and reagents (I55 and 1-aminocyclopropane-1-carboxylic acid, methylester hydrochloride)

The residue was purified once by silica gel chromatography using a gradient of dichloromethane containing 0 to 10% methanol and by HPLC (Hypersil Column) with a gradient acetonitrile/water 95/5 to 5/95 to afford the desired product.

Yield: 32%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.12-1.20 (m, 2H), 1.33-1.50 (m, 4H), 1.50-1.70 (m, 6H), 3.03-3.12 (m, 1H), 3.52 (s, 3H),

3.60 (s, 1H), 3.89-3.98 (m, 1H), 4.40 (d, 1H), 7.72 (dd, 2H), 7.94 (d, 2H), 9.17 (s, 1H).
MS (m/z) / M+1= 431
HPLC (uv purity, λ= 214 nm)= 97.9%

Example I63: R1= cyclopentyl, R2= methyl, R3= 4-benzamide
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzamide

To a solution of compound I42 (0.53 mmol, 150 mg) in ethanol (17 ml), a solution of Na_2CO_3 [3N] (5.6 mmol, 1.88 ml) and a solution of H_2O_2 at 30% in water (1.54 ml) were added. The solution was stirred overnight at room temperature. To the mixture, was added a solution of H_2O_2 at 30% in water (770 μl) and the solution was allowed to stir at room temperature during two days (reaction to completion). The resultant mixture was concentrated by distillation of the solvent and the crude material was precipitated in water. The precipitate was filtered off, washed several times with water and dried to give the pure product.
Yield= 53.4%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.43-1.95 (m, 8H), 3.18-3.28 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.70 (dd, 2H), 7.95 (dd,2H), 8.05 (s, 1H).
MS (m/z) / M+1= 303
HPLC (uv purity, λ= 214 nm)= 98.04%

Example I64: R1= cycloheptyl, R2= methyl, R3= 4-benzamide
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

Compound I64 was prepared by the procedure described in example I63 using appropriate intermediates (I43) and reagents.
The precipitate was filtered, washed several times with water and dried to give the pure product.
Yield= 59.88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.83 (m, 12H), 2.78-2.85 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.97 (dd,2H), 8.07 (s, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 98.98%

Example I65: R1= 4-fluoro-phenyl, R2= methyl, R3= 4-benzamide

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I65 was prepared by the procedure described in example I63 using appropriate intermediates I44 and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 72.43%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.02-7.40(m, 2H), 7.15-7.24 (m, 2H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.95 (dd,2H), 8.05 (s, 1H).

MS (m/z) / M+1= 329

HPLC (uv purity, λ= 214 nm)= 97.7%

Example I66: R1= 3-hydroxy-phenyl, R2= methyl, R3= 4-benzamide

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I66 was prepared by the procedure described in example I63 using appropriate intermediates (I45) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 59.84%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.70 (s, 3H), 6.44-6.52 (m, 3H), 7.18 (t, 1H), 7.44 (s, 1H), 7.75 (dd, 2H), 7.97 (dd, 2H), 8.06 (s, 1H), 9.40 (s, 1H).

MS (m/z) / M+1= 327

HPLC (uv purity, λ= 214 nm)= 99.68%

Example I67: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-benzamide

5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

Compound I67 was prepared by the procedure described in example I63 using appropriate intermediate (I46) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 44.41%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.25-7.32 (m, 2H), 7.43-7.50 (m, 2H), 7.78 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H), 13.30 (b, 1H).

MS (m/z) / M+1= 373

HPLC (uv purity, λ = 214 nm)= 90.52%

Example I68: R1= trans-4-methyl-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I68 was prepared by the procedure described in example I63 using appropriate intermediates (I47b) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 52.53%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.90 (d, 3H), 0.95-1.08 (m, 2H), 1.30-1.45 (m, 3H), 1.67-1.85 (m, 4H), 2.50-2.60 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 99.7%

Example I69: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of I48 (0.477 mmol, 150 mg) in ethanol (17 ml), a solution of Na_2CO_3 [3N] (5.1 mmol, 1.7 ml) and a solution of H_2O_2 at 30% in water (1.4 ml) were added and the mixture was stirred overnight at room temperature. This mixture was poured into water before extraction with ethyl acetate. The organic layer was washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue wich was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 to 98/2) to afford the pure product.

Yield= 31%

^{1}H-NMR(400MHz, DMSO) δ ppm: 1.20-1.42 (m, 4H), 1.75-1.90 (m, 4H), 2.50-2.63 (m, 1H), 3.40-3.52 (m,1H), 3.50 (s, 3H), 4.55 (s,1H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.98 (dd, 2H), 8.07 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm)= 97.3%

Example I70: R1= bicyclo[2.2.1]hept-2-yl, R2= methyl, R3= 4-benzamide

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I70 was prepared by the procedure described in example I69 using appropriate intermediates (I49) and reagents.

The residue was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 to 90/10)to afford the desired product.

Yield= 66%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.25 (m,3H), 1.28-1.40 (m,1H), 1.40-1.67 (m,4H), 2.10-2.18 (m,1H), 2.25-2.32 (m,1H), (2.70-2.80 (m,1H), 3.52 (s, 3H), 7.50 (s, 1H), 7.72 (dd, 2H), 7.97 (dd, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 329

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I71: R1= (1R*,2R*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,2R*)-2-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I71 was prepared by the procedure described in example I69 using appropriate intermediates (I50) and reagents.

The residue was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 to 90/10)to afford the pure product.

Yield= 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.39 (m, 4H), 1.60-1.75 (m, 3H), 1.80-1.90 (m,1H), 2.35-2.45 (m, 1H), 3.50 (s, 3H), 4.55 (s,1H), 7.50 (s, 1H), 7.72 (dd, 2H), 7.96 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1=333

HPLC (uv purity, λ= 214 nm)= 97.4%

Example I72: R1= (1R*,2S*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of I51 (0.16 mmol, 50 mg) in DMSO (100 μl), K_2CO_3 (0.022 mmol, 3 mg), a solution of H_2O_2 at 30% in water (20 μl) was added and the mixture was stirred overnight at room temperature. To this mixture, water was added and the solution was allowed to stir 15 minutes. The precipitate was filtered off and dried under reduced pressure to give the desired product.

Yield= 68%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.38 (m, 2H), 1.40-1.80 (m, 6H), 2.85-2.90 (m, 1H), 3.57 (s, 3H), 3.60-3.68 (m, 1H), 4.10 (d,1H), 7.40 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1= 333

HPLC (uv purity, λ= 214 nm)= 98.8%

Example I73: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I73 was prepared by the procedure described in example I69 using appropriate intermediates (I52-a) and reagents.

The mixture was concentrated under reduced pressure and stirred in water several hours, filtered and dried under vaccum to afford the desired product.

Yield= 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.30-1.70 (m, 8H), 3.10 (s, 1H), 3.52 (s, 3H), 3.93 (s,1H), 4.42 (d, 1H), 7.43 (s, 1H), 7.70 (dd, 2H), 7.96 (dd,2H), 8.05 (s, 1H).

MS (m/z) / M+1=333

HPLC (uv purity, λ= 214 nm)= 98.3%

Example I74: R1= (1R*,3S*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I74 was prepared by the procedure described in example I69 using appropriate intermediates (I52-b) and reagents.

The mixture was concentrated under reduced pressure and stirred in water several hours, filtered and dried under vaccum to afford the desired product.

Yield= 83%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.30 (m, 4H), 1.65-1.78 (m, 2H), 1.78-1.88 (m, 1H), 1.95-2.05 (m, 1H), 3.40-3.58 (m, 4H), 4.60 (s, 1H), 7.45 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1=333

HPLC (uv purity, λ= 214 nm)= 99.4%

Example I74.1: R1= 3-oxo-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I74 (0.15 mmol, 50 mg) in dichloromethane (0.5 ml), tetrapropylammoniumperruthenate (0.5% mol, 3 mg), 4-methylmorpholine-N-oxide (0.22 mmol, 28 mg) and molecular sieve (500 mg/mol, 75 mg) were added and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of silica gel (eluted with dichloromethane/methanol 100/0 to 95/5), the filtrate was concentrated under reduced pressure and washed with diethylether to afford the pure product.

Yield= 18%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.63-1.82 (m, 2H), 1.89-2.10 (m, 2H), 2.21-2.50 (m, 4H), 3.15-3.30 (m, 1H), 3.52 (s, 3H), 7.45 (s, 1H), 7.70 (dd, 2H), 7.98 (dd, 2H), 8.08 (s, 1H).

MS (m/z) / M+1=331

HPLC (uv purity, λ= 214 nm)= 98.7%

Example I75: R1= 3,3-difluoro-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I52-b (0.318 mmol, 100 mg) in dichloromethane (1 ml) was added tetrapropylammonium perruthenate (0.5 %mol,6 mg), 4-methylmorpholine-N-oxide (0.477 mmol, 56 mg) and molecular sieve (500 mg/mol, 160 mg). The mixture was stirred at room temperature for 3H, filtered through silica gel (eluted with cyclohexane/ethyl acetate 100/0 to 60/40) and concentrated under reduced pressure to afford 4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Yield = 90%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.60-1.80 (m, 2H), 1.87-2.10 (m, 2H), 2.21-2.30 (m, 3H), 2.55-2.60 (m, 1H), 3.15 (s, 1H), 3.52 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H).

To a solution of this ketone (0.288 mmol, 90 mg) in dichloromethane (0.5 ml), a solution of deoxo-fluor (0.49 mmol, 90 μl) in dichloromethane (1 ml) and ethanol (0.346 mmol, 5 μl) was added and the mixture was stirred overnight at room temperature. The mixture was poured into a satured solution of $NaHCO_3$ (pH=7), and the aqueous layer was extrated with dichloromethane. The organic layer was washed with water and brine, dried with magnesium sulfate, filtered and concentrated under reduced pressure to give a residue wich was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate 100/0 to 80/20)to afford the pure di-fluoro compound : 4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Yield = 12%

^{1}H-RMN (400MHz, DMSO) δ ppm: 1.40-1.55 (m, 2H), 1.78-1.90 (m, 4H), 1.95-2.09 (m, 1H), 2.15-2.28 (m, 1H), 2.80-2.90 (m, 1H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H).

To a solution of this di-fluoro derivative (0.036 mmol, 12 mg) in ethanol (1.6 ml) a solution of Na_2CO_3 [3N] (0.6 mmol, 200 μl), and a solution of H_2O_2 at 30% in water (150μl) were added and the mixture was stirred at 40°C overnight. Then, a solution of H_2O_2 at 30% in water (130 μl) was added and the solution was allowed to stir 12 h at 40°C. The mixture was concentrated under reduced pressure. The residue was stirred in water several hours, filtered, washed with ether and dried under vaccum to give the desired compound.

Yield= 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.33-1.53 (m, 2H), 1.70-1.90 (m, 4H), 1.90-2.05 (m, 1H), 2.15-2.28 (m, 1H), 2.80-2.90 (m, 1H), 3.55 (s, 3H), 7.48 (s, 1H), 7.72 (dd, 2H), 7.96 (dd, 2H), 8.08 (s, 1H)

MS (m/z) / M+1=353

HPLC (uv purity, λ = 214 nm)= 98.7%

Example I76: R1= (1R*,3R*)-3-fluoro-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I52-b (1.59 mmol, 500 mg) in dichloromethane (4 ml), 4-morpholinisulfurtrifluoride (3.18 mmol, 390 μl) was added at -15°C dropwise under nitrogen atmosphere. The mixture was warmed at room temperature during 30 minutes and poured into a saturated solution of $NaHCO_3$ (pH=7). The aqueous phase was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduce pressure to give a residue wich was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate 100/0 to 70/30) to afford 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile and a mono-fluoro intermediate (4-[5-((trans)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile):

Yield= 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.50 (m, 1H), 1.58-1.85 (m, 6H), 1.92-2.05 (m, 1H), 2.95-3.05 (m, 1H), 3.55 (s, 3H), 4.95 (d, 1H), 7.83 (dd, 2H), 7.95 (dd, 2H).

To a solution of this fluoro intermediate (0.2 mmol, 65 mg) in ethanol (8.7 ml) a solution of Na_2CO_3 [3N] (2.61 mmol, 870 μl) and a solution of H_2O_2 at 30% in water (705 μl) were added and the mixture was stirred overnight at 40°C. A solution of H_2O_2 at 30% in water (705 μl) was added and the reaction was allowed to stir for 10h at 40°C. The mixture was concentrated under reduced pressure. The residue was stirred in water several hours, filtered, washed with ether and dried under vaccum to give the title product I76.

Yield= 58%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.35-1.52 (m, 1H), 1.52-1.90 (m, 6H), 1.90-2.08 (m, 1H), 2.93-3.08 (m, 1H), 3.55 (s, 3H),

5.00 (d, 1H), 7.50 (s, 1H), 7.78 (dd, 2H), 7.99 (dd, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 335

HPLC (uv purity, λ= 214 nm)= 96.6%

Example I77: R1= 3-cyclohexene, R2= methyl, R3= 4-benzamide 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile from protocol I76 (0.94 mmol, 280 mg) in ethanol (41 ml), a solution of Na_2CO_3 [3N] (12.3 mmol, 4.1 ml), and a solution of H_2O_2 at 30% in water (3.33 ml) were added. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was stirred in water several hours, filtered, and dried under vaccum to afford the pure product.

Yield= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.48-1.65 (m, 1H), 1.72-2.35 (m, 5H), 2.82-2.92 (m, 1H), 3.55 (s, 3H), 5.65 (t, 2H), 7.50 (s, 1H), 7.71 (dd, 2H), 7.95 (dd, 2H), 8.09 (s, 1H)

MS (m/z) / M+1= 315

HPLC (uv purity, λ= 214 nm)= 96.1%

Example I78: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(1H-tetrazol-5-yl)-phenyl (1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol

To a solution of I52-a (1.27 mmol, 400 mg) in toluene (3 ml), sodium azide (1.65 mmol, 108 mg) and triethylamine hydrochloride (1.65 mmol, 228 mg) were added and the mixture was warmed at reflux during 24 hours. The reaction mixture was cooled at room temperature, acidified with a solution of HCl [0.1N], and then basified at pH=6-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane and the organic layer was washed with a saturated solution of NaCl, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The

residue was chromatographed on silica gel column using a gradient of dichloromethane containing from 0 to 20% methanol to afford the title compound.

Yield: 50%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 8H), 3.00-3.15 (m, 1H), 3.50 (s, 3H), 3.85-3.98 (m, 1H), 4.40 (s, 1H), 7.75 (dd, 2H), 8.10 (d, 2H).

MS (m/z) / M+1= 358

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I79: R1= 3-(6-hydroxy)-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid

The title compound was prepared by the procedure desribed in example I3 using ethanol as solvent and appropriate intermediates and reagents. The residue was twice chromatographed on silica gel eluting with dichloromethane containing from 0 to 7% of methanol. The isolated product was washed with water to afford the desired product.

Yield= 9.7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.62 (s, 3H), 6.80 (t, 1H), 7.12 (d, 1H), 7.40-7.46 (m, 3H), 7.59 (d, 2H).

MS (m/z) / M+1 =362/364.

HPLC (uv purity, λ= 214 nm): 98.36%

Example I80 : R1= 3-benzoic acid, R2= methyl, R3= 4-cyano-phenyl

3-[5-(4-cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A suspension of 1,3,4-thiadiazolium perchlorate (3c) (4.873 mmol, 1.70 g), 3-aminobenzoic acid (4.87 mmol, 0.668 g) and triethylamine (4.873 mmol, 0.679 ml) in ethanol (20 ml) was refluxed for 3.5h. On cooling, the solid formed was filtered off and washed with cold EtOH and ether. The solid was dried under reduced pressure to give 1.25 g of the expected compound.

Yield= 76.2%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.87 (s, 3H), 7.39-7.42 (m, 1H), 7.60-7.65 (m, 1H), 7.70 (s, 1H), 7.78-7.82 (m, 1H), 7.96-8.00 (d, 2H), 8.00-8.04 (d, 2H).

MS (m/z) / M+1 = 337/338

HPLC (uv purity, λ= 214 nm)= 93.22%

Example I80.1: R1= 3-benzoic acid, R2= methyl, R3= 4-benzamide

3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

Concentrated sulfuric acid (19.8 mmol, 1.06 ml) and water (0.13 ml) were respectively added, at 0°C, to I80 (0.595 mmol, 0.200 g) and the reaction mixture was heated at 80°C for 1h30. Then, ice was added to the mixture and the formed precipitate was filtered off and purified by chromatography on silica gel, eluting with a mixture of acetic acid/dicloromethane/methanol (1.5/85/13.5). The isolated product was triturated in methanol and the solid was filtered off and dried under vaccum to give the title product.

Yield=34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.76 (s, 3H), 7.30 (d, 1H), 7.46-7.55 (m, 2H), 7.62 (s, 1H), 7.67 (d, 1H), 7.80 (d, 2H), 7.99 (d, 2H), 8.09 (s, 1H), 12.90-13.02 (d, 1H).

MS (m/z) / M+1= 355/356

HPLC (uv purity, λ= 214 nm): 96.37%

Example I81: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-(methylsulfonyl)-phenyl

2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I81 was prepared by the procedure described in example I4 (protocol A) with the appropriate reagents and using 1.0 eq of triethylamine. The reaction mixture was concentrated and the residue was purified by silica gel chromatography

eluting with dichloromethane and then a mixture of dichloromethane/ MeOH/AcOH (98 /1.8 /0.2).

Yield= 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.19 (s, 3H), 3.57 (s, 3H), 7.11-7.19 (m, 2H), 7.31-7.34 (m, 1H), 3.50 , 7.79 (d, 2H), 7.85 (d, 2H), 13.08-13.14 (b, 1H).

MS (m/z) / M+1 = 408/409

HPLC (uv purity, λ= 214 nm)= 98.3%

Example I82: R1= 3-carboxylic acid cyclohexyl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl

3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid

I82 was prepared by the procedure described in example I4 with the appropriate reagents and using 1.0 eq of triethylamine. The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography eluting with $CHCl_3$/MeOH (93/7) to afford 15 mg of the desired product.

Yield= 1.52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.02-1.24 (m, 4H), 1.58-1.70 (m, 3H), 1.80-1.86 (m, 1H), 2.12-2.19 (m, 1H), 2.44-2.52 (m, 1H), 3.06 (s, 3H), 3.36 (s, 3H), 7.70 (d, 2H), 7.82 (d, 2H), 11.82-11.90 (b, 1H).

MS (m/z) / M+1 = 395/396

HPLC (uv purity, λ= 214 nm): 98.76%

Example I83: R1= piperidin-1-yl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl

[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine

To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (1.26 mmol, 0.5 g) in ethanol (6 ml) were added 1-aminopiperidine (2.5 mmol, 0.3 ml) then triethylamine (2.5 mmol, 0.4 ml) and the mixture was maintained at 70°C for 3 hours. The mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed twice

with water, concentrated under reduced pressure and purified by chromatography on silica gel (99:1 DCM/MeOH) to give 0.2 g of the title compound.

Yield = 45%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.46 (s, 2H), 1.68-1.71 (m, 4H), 2.77 (s, 4H), 3.07 (s, 3H), 3.65 (s, 3H), 7.81-7.83 (dd, 2H), 7.95-7.97 (dd, 2H).

MS (m/z) / M+1= 353.46.

HPLC (uv purity, λ= 214 nm)= 97.4%

Example I84: R1= tetrahydro-pyran-4-yl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl

[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine

To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (0.7 mmol, 0.3 g) in ethanol (4 ml) were added 4-aminotetrahydropyran (1.4 mmol, 0.3 g) and triethylamine (3 mmol, 0.4 ml). The mixture was maintained for 3 hours at 70°C, concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (99:1 DCM/MeOH) and washed with ethyl acetate and heptane to give 23 mg of the expected compound.

Yield= 30%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.68-1.85 (m, 4H), 2.88-2.95 (m, 1H), 3.07 (s, 3H), 3.47-3.57 (m, 2H), 3.65 (s, 3H), 4.01-4.06 (m, 2H), 7.81 (d, 2H), 7.97 (d, 2H).

MS (m/z) / M+1= 354.03

HPLC (uv purity, λ= 214 nm)= 100%.

Example I85: R1= 3-benzoic acid, R2= methyl, R3= 4-acetylamino-phenyl

3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A suspension of 1,3,4-thiadiazolium triflate (3d) (0.7 mmol, 0.3 g), triethylamine (2.1 mmol, 0.3 ml) and 3-

acetamidobenzoic acid (0.6 mmol, 0.077 g) in ethanol (20 ml) was refluxed overnight. The mixture was concentrated under reduced pressure, purified by chromatography on silica gel (95:5 DCM /MeOH) and washed with MeOH to give 0.01 g of a white solid.

Yield= 5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.06 (s, 3H), 2.71 (s, 3H), 7.26 (d, 1H), 7.47 (t, 1H), 7.60-7.70 (m, 6H), 10.18 (s, 1H).

MS (m/z) / M+1=368.95

HPLC (uv purity, λ= 214 nm)= 98%

Example I86: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

A mixture of trans-4-aminocyclohexanol (0.28 mmol, 0.04 g), triethylamine (0.39 mmol, 0.06 ml) and 3-methyl-2-methylthio[1,3,4]thiadiazolium triflate (3d) (0.14 mmol, 0.05 g) were refluxed in ethanol (1ml) overnight. The mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (95:5 DCM /MeOH) to give 0.014g of a white solid.

Yield= 30%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.23-1.38 (m, 4H), 1.76-1.86 (m, 4H), 2.06 (s, 3H), 2.45-2.60 (m, 1H), 4.52 (d, 1H), 3.38-3.44 (m, 1H), 3.47 (m, 3H), 7.58 (d, 2H), 7.68 (d, 2H), 10.15 (s, 1H).

MS (m/z) / M+1 = 346.87

HPLC (uv purity, λ= 214 nm)= 98.5%

Example I87: R1= (1R*,3S*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

I87 was prepared by the procedure described in example I86 (protocol A).

I87 was purified by chromatography on silica gel with AcOEt:Cyclohexane (80:20) and washed with MeOH to give 0.15g of the expected compound.

Yield= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.30 (m, 4H), 1.55-2.00 (m, 4H), 2.10 (s, 3H), 2.60 (m, 1H), 3.50 (m, 1H), 3.50 (s, 3H), 4.6 (d, 1H), 7.60 (dd, 2H), 7.60 (dd, 2H), 10.15 (s,1H).

M+1 = 347.1

Example I88: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-((1R*,3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

To a suspension of I87 (0.4 mmol, 0.15 g) in DCM (2 ml) containing 4Å molecular sieves (0.216 g), N-methyl morpholine oxide (0.65 mmol, 0.76 g) under nitrogen atmosphere was added tetrapropylammonium perruthenate (10% mol equiv., 15 mg). The resulting mixture was stirred overnight, filtered, washed with methanol and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with DCM:MeOH (95:5) to give 0.1 g of a ketone intermediate: N-{4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

Yield= 71%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25 (m, 1H), 1.60-1.75 (m, 2H), 1.85-2 (m, 2H), 2.05 (s, 3H), 2.3 (m, 3H), 3.15 (m,1H), 3.5 (s, 3H), 7.55 (dd, 2H), 7.70 (dd, 2H), 10.15 (s,1H).

To a solution of this ketone intermediate (0.15 mmol, 0.05 g) in THF (2 ml) at -70°C under nitrogen atmosphere was added a 1M solution of L-Selectride in THF (0.2 mmol, 0.2 mL). The resulting mixture was allowed to warm up to room temperature over 1 hour, diluted with dichloromethane, washed with water and concentrated under reduced pressure.

The residue was purified by chromatography on silica gel with AcOEt:Cyclohexane (80:20) to give 30 mg of the expected product.

Yield= 60%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.25-1.30 (m, 3H), 1.72-1.78 (m, 5H), 2.20 (s, 3H), 3.11-3.14 (m, 1H), 3.58 (s, 3H), 4.13 (m, 1H), 7.20 (s, 1H), 7.52-7.60 (m, 4H).

MS (m/z) / M+1= 347.21

HPLC (uv purity, λ= 214 nm)= 98%

Example I89 : R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-pyridin-3-yl

***N*-{5-[5-((1R*,3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide**

The compound I89 was prepared by the procedure described in example I4 (protocol A).

To a suspension of 1,3,4-thiadiazolium perchlorate (3e) (0.5 mmol, 2 g) in ethanol (20 ml) were added triethylamine (1.5 mmol, 2 ml) followed by 3-aminocyclohexanol (0.8 mmol, 0.9 ml) and the mixture was maintained at 70°C overnight, concentrated under reduced pressure. The residue was taken into dichloromethane, washed twice with water, concentrated under reduced pressure and purified by chromatography on silica gel (20:80 cyclohexane /EtOAc) to give 0.03g of a white solid.

Yield= 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.37-1.65 (m, 8H), 2.11 (s, 3H), 3.03-308 (m, 1H), 3.50 (s, 3H), 3.91-3.92 (m, 1H), 4.41 (d, 1H), 8.01-8.03 (dd, 1H), 8.17 (d, 1H), 8.55 (d, 1H), 10.75 (s, 1H).

MS (m/z) / M+1= 348.3

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I90: R1= 3-cyano-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile

To a suspension of I6.11 (4.14 mmol, 1.43 g) in pyridin (20 mL) was added benzoyl chloride (8.28 mmol, 964 µL). The mixture was heated at reflux for 2 days.

The solvent was concentrated under reduced pressure, the reaction mixture was retaken in an aqueous solution of $NaHCO_3$ and the crude product was extracted with dichloromethane. The compound was purified by chromatography on silica gel (eluted with cyclohexane/ethyl acetate: 80/20 to 70/30) to give 1.25 g of the expected compound (92%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.40 (d, 1H), 7.48 (s, 1H), 7.52-7.60 (m, 4H), 7.73 (d, 2H).

MS (m/z) / M+1= 327/329

HPLC (uv purity, λ= 245nm)= 99.4%

Example I90.1: R1= 3-(1H-Tetrazol-5-yl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine

A mixture of I90 (1.22 mmol, 0.4 g), sodium azide (1.59 mmol, 0.1 g) and triethylamine hydrochloride (1.59 mmol, 0.22 g) in toluene (7 mL) was heated at 90°C with stirring under nitrogen atmosphere. After cooling, the reaction mixture was poured in water and extracted with dichloromethane. To the aqueous layer, aqueous HCl 0.1N was added until the pH is acidic (CAUTION! This has to be done under a well ventilated hood). The precipitate was filtered, washed with ether and the resulting compound was cristallized in dichloromethane containing few drops of methanol to give 0.1 g of the desired compound

Yield: 24%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.28 (d, 1H), 7.55 (d, 2H), 7.60 (t, 1H), 7.70-7.77 (m, 4H)

MS (m/z) / M+1 = 370/372

HPLC (uv purity, λ= 245 nm)= 99.7%

Example I90.2: R1= 3-(N-Hydroxycarbamimidoyl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine

To a mixture of I90 (1.53 mmol, 0.5 g) and hydroxylamine hydrochloride (2.29 mmol, 0.156 g) in ethanol (13 mL) was added sodium hydroxyde (2.29 mmol, 0.09 g) dissolved in the minimum of water. The reaction mixture was heated at reflux for 24h with stirring. After cooling, the precipitate is filtered, washed with ethanol and dried under vacuum at 45°C to give 0.54 g of the desired compound

Yield: 98%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 5.76 (bs, 2H), 7.05 (dd, 1H), 7.34-7.4 (m, 3H), 7.54 (d, 2H), 7.70 (d, 2H), 9.6 (s, 1H).

MS (m/z) / M+1= 360/362

HPLC (uv purity, λ= 245 nm)= 97.3%

Example I90.3: R1= 3-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol

A mixture of I90.2 (2.78 mmol, 0.1 g) and 1,1'-carbonyldiimidazole (5.56 mmol, 0.9 g) in anhydrous THF (2 mL) was heated at reflux for 5h. After cooling, the reaction mixture was concentrated and poured in water. Dichloromethane was added and the precipitate was filtered and washed with methanol. The resulting mixture was purified by chromatography on silica gel (eluent dichloromethane/methanol: 98/2 + 1% acetic acid) to give 0.03 g of the desired product.

Yield: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.20 (dt, 1H), 7.50-7.55(m, 5H), 7.70 (d, 2H).

MS (m/z) / M+1 = 386/388

HPLC (uv purity, λ= 245 nm)= 98.2%

EXAMPLE I: PROTOCOL C

Example I91: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-bromo-phenyl

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I91 was prepared by the procedure described in example I18 (Protocol C)using appropriate intermediates and reagents.

Yield= 50.4 %

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.51 (m, 5H), 1.64-1.70 (m, 1H), 1.78-1.89 (m, 4H), 2.38 (s, 3H), 2.56-2.64 (m, 1H), 3.55 (s, 3H), 7.28 (d, 1H), 7.47 (s, 1H), 7.54 (d, 1H).

MS (m/z) / M+1= 366/368

Example I91.1: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-cyano-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile

To a solution of I91 (7.370 mmol, 2.7 g) in N-methyl-2-pyrrolidone (17ml), copper cyanide (13.267 mmol, 1.19 g) was added and the mixture was heated at reflux for 3h. The mixture was cooled at room temperature, basified with a solution of aqueous ammonia (2N) and stirred 10h at room temperature. The suspension was then filtered through Celite and the aqueous layer was extracted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 1% of methanol.

Yield= 54.8

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.59 (m, 5H), 1.64-1.67 (m, 1H), 1.77-1.87 (m, 4H), 2.57-2.67 (m, 4H), 3.60 (s, 3H), 7.52 (d, 1H), 7.56 (s, 1H), 7.63 (d, 1H).

Example I91.2: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide

To a solution of I91.1 (0.320 mmol, 0.1 g) in ethanol (17 ml), an aqueous solution of sodium carbonate 3N (3.424 mmol, 1.14 ml) then a solution of hydrogen peroxide (5.60 ml) were added. The suspension was stirred for 2 days at room temperature, then heated at 40°C for 8h. The mixture was poured into a solution of $Na_2S_2O_5$ and evaporated to dryness then the crude material was diluted with water and extracted with dicloromethane. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Yield: 70%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.51 (m, 5H), 1.60-1.68 (m, 1H), 1.81-1.91 (m, 4H), 2.52 (s, 3H), 2.59-2.69 (m, 1H), 3.60 (m, 3H), 5.64-5.83 (b, 2H), 7.49 (s, 2H), 7.48 (s, 1H).

MS (m/z) / M+1= 331/332.

HPLC (uv purity, λ= 214 nm): 97.28%

Example I92: R1= cyclohexyl, R2= methyl, R3= 4-bromo-3-methoxy-phenyl

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-hydroxybenzoic acid (14.480 mmol, 2 g) in acetic acid (14.5 ml) and sulfuric acid (1.5 ml) at 50°C, a solution of bromine (15.204 mmol, 0.780 ml) in acetic acid (7.2 ml) was added and stirred 30 min at 100°C. The reaction was allowed to room temperature and diluted with water. The aqueous layer was extracted with ethylacetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the 4-Bromo-2-hydroxy-benzoic acid (yield =100%).

To a solution of 4-bromo-3-hydroxybenzoic acid (14.480 mmol, 2.600 g) in acetone (180 ml), potassium carbonate (62.988 mmol, 8.710 g) and dimethylsulfate (31.422 mmol, 2.970 ml) were added. The reaction was stirred at room temperature for 30 min and evaporated to dryness.The residue was then diluted with water and extracted with ethylacetate. The collected organic layer was washed with water and brine,

dried (MgSO$_4$), filtered and concentrated under reduced pressure. 4-Bromo-3-methoxy-benzoic acid methyl ester was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 20% ethylacetate (yield= 47%).

To a solution of 4-Bromo-3-methoxy-benzoic acid methyl ester (6.875 mmol, 1.676 ml) in a mixture 1/1 of THF/ MeOH (15ml), lithium hydroxyde (7.553 mmol, 0.180 g) was added and the reaction was stirred at room temperature overnight before distillation of volatiles. The residue was diluted with water, acidified with a solution of HCl (1N) and stirred for 1h. The formed precipitate was filtered off, washed with water and petroleum ether to give 4-Bromo-3-methoxy-benzoic acid (Yield = 56%).

The title compound was prepared by procedure as described in example I17 (protocol C) starting from 4-Bromo-3-methoxy-benzoic acid. In this particular case, methyltrifluoromethanesulfonate (1.2eq) was added once and the basic aqueous layer was extracted with DCM. The crude was chromatographed on silica gel eluting with cyclohexane containing from 0 to 10% ethylacetate. The oil obtained was triturated in diethylether and the formed white solid was isolated by filtration.

Yield = 26% (overall, the 2 steps).

^{1}H-NMR (400MHz, CDCl$_3$) δ ppm: 1.20-1.46 (m, 5H), 1.60-1.68 (m, 1H), 1.77-1.88 (m, 4H), 2.58-2.68 (m, 1H), 3.59 (s, 3H), 3.96 (s, 3H), 7.02 (d, 1H), 7.22 (s, 1H), 7.53 (d, 1H)

Example I92.1: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide

I92 was reacted with copper cyanide by the procedure described in example I91-1 and the formed intermediate was transformed to I92.1 following the following protocol:

To a heterogeneous solution of this material (0.9134 mmol, 0.300 g) in ethanol (50 ml), a solution of sodium carbonate (3N) (9.773 mmol, 3.258 ml) and hydrogen peroxide (13.3 ml)

were added and the reaction was heated at 40°C for 1.5 days. The mixture was poured into a saturated solution of $Na_2S_2O_5$ and the solution was concentrated under reduced pressure. The residue was diluted with water, extracted with dichloromethane and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The crude material was purified by chromatography on silica gel eluting with dichloromethane containing from 0 to 4% methanol.

Yield: 25%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.76-1.88 (m, 4H), 2.59-2.69 (m, 1H), 3.60 (s, 3H), 4.02(s, 3H), 5.80-5.90 (b, 1H), 7.25 (d, 1H), 7.34 (s, 1H), 7.62-7.67 (b, 1H), 8.23 (d, 1H).

MS (m/z) / M+1= 347/348

HPLC (uv purity, λ= 214 nm): 97.61%

Example I92.2: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide

To a mixture of I92.1 and n-tetrabutylammonium iodide (0.433 mmol, 0.160 g) in anhydrous dichloromethane (2 ml) under nitrogen atmosphere at -78°C, a solution of BCl_3 1N in dichloromethane (0.433 mmol, 0433 ml) was added and the reaction mixture was allowed to stir at -78°C for 10 min followed by 2h at 0°C and 1h30 at room temperature. Then, a solution of BCl_3 1N in dichloromethane (0.433 mmol, 0433 ml) was added. After an additionnal 1h30 of stirring at room temperature, the reaction was quenched with water and basified with a saturated solution of sodium bicarbonate before extraction with dicloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane containing from 0 to 4% of methanol to give the desired product.

Yield= 26%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.50 (m, 5H), 1.63-1.70 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.68 (m, 1H), 3.60 (s, 3H), 5.70-6.20 (b, 2H), 7.18 (s, 1H), 7.24 (d, 1H), 7.38 (d, 1H), 12.25 (s, 1H).

MS (m/z) / M+1= 333/334

HPLC (uv purity, λ= 214 nm): 96.54%

Example I93: R1= cyclohexyl, R2= methyl, R3= 3-nitro-4-methoxycarbonyl-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester

I93 was prepared by the procedure described in example I21 (protocol C) using the appropriate intermediates and reagents. In this particular case, triethylamine was not used and the expected product was isolated by filtration after treatment with a saturated solution of $NaHCO_3$.

Yield= 77%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.48 (m, 5H), 1.64-1.70 (m, 1H), 1.80-1.90 (m, 4H), 5.58-5.66 (m, 1H), 3.63 (s, 3H), 3.82 (s, 3H), 7.80-7.84 (m, 2H), 8.11 (s, 1H).

Example I93.1: R1= cyclohexyl, R2= methyl, R3= 3-amino-4-methoxycarbonyl-phenyl

2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a solution of I93 (1.328 mmol, 0.500 g) in ethanol (20 ml), tin chloride dihydrate (6.641 mmol, 1.495 g) was added and the mixture was heated at reflux for 5h then allowed to stand at room temperature overnight. The mixture was evaporated to dryness and the crude material was basified with a saturated solution of sodium carbonate before extraction with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vaccum. The residue was chromagraphed on silica gel eluting with dicloromethane containing from 0 to 2% of methanol to afford the desired compound.

Yield: 65%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.69 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.67 (m, 1H), 3.60 (s, 3H), 3.89(s, 3H), 5.77-5.83 (b, 2H), 7.88-7.92 (m, 2H), 7.89 (d, 1H).

MS (m/z) / M+1= 347/349

HPLC (uv purity, λ= 214 nm): 98.31%

Example I93.2: R1= cyclohexyl, R2= methyl, R3= 3-acetylamino-4-methoxycarbonyl-phenyl

2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a suspension of I93.1 (0.144 mmol, 0.05 g) in anhydrous toluene (2 ml) at 0°C, triethylamine (0.150 mmol, 0.015 ml) and acetic anhydride (0.160 mmol, 0.015 ml) were added. The reaction was allowed to stir at room temperature for 3 days and 5.4 more equivalents of acetic anhydride and triethylamine were added. After 2 days of stirring at room temperature the mixture was evaporated to dryness and the residue was chromatographed on silica gel eluting with dichloromethane containing from 0 to 1% of methanol.

Yield = 89%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.67 (m, 1H), 1.76-1.88 (m, 4H), 2.28 (s, 3H), 2.60-2.70 (m, 1H), 3.60 (s, 3H), 3.93 (s, 3H), 7.45 (d, 1H), 8.03 (d, 1H), 8.98 (s, 1H), 11.10 (s, 1H).

MS (m/z) / M+1= 389/390

HPLC (uv purity, λ=214 nm): 96.93%

Example I93.3: R1= cyclohexyl, R2= methyl, R3= 3-amino-4-benzamide

2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I93 was modified following the procedure described in example I37.3 to afford the amide derivative with an overall yield 84%. The reduction of the nitro group to give I93.3 was performed as described in example I93.1. In this particular case, the reactionnal mixture was basified with a

saturated solution of sodium carbonate then distilled. The crude was diluted in water and extracted with dicloromethane. The aqueous phase, saturated with brine, was then extracted with ethylacetate and the organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give a residue which was purified by two consecutive chromatographies on silica gel, eluting first with dichloromethane/methanol (93/7) and the second purification made eluting with a gradient of cyclohexane containing from 0 to 40% ethylacetate.

Yield= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.27-1.40 (m, 5H), 1.56-1.62 (m, 1H), 1.70-1.80 (m, 4H), 2.58-2.65 (m, 1H), 3.50 (s, 3H), 6.73-6.78 (m, 3H), 7.00 (s, 1H), 7.10-7.20 (b, 1H), 7.61 (d, 1H), 7.75-7.85 (b, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm): 95.83%

Example I93.4: R1= cyclohexyl, R2= methyl, R3= 4-oxo-3,4-dihydro-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one

A mixture of I93.1 (1.443 mmol, 0.500 g) and formamide (4 ml) was stirred and heated at reflux for 2h before cooling at room temperature. The mixture was diluted with water and the precipitate was collected by filtration. The precipitate was washed with water and petroleum ether and purified by chromatography on silica gel, eluting with dichloromethane containing from 0 to 3% of methanol followed by an isocratic elution with dichloromethane/methanol (93/7).

Yield= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.55-1.64 (m, 1H), 1.70-1.83 (m, 4H), 2.63-2.71 (m, 1H), 3.56 (s, 3H), 7.73 (s, 1H), 7.00 (s, 1H), 7.80 (d, 1H), 8.12-8.19 (m, 3H), 12.30-12.40 (b, 1H).

MS (m/z) / M+1= 342/343

HPLC (uv purity, λ= 214 nm): 95.19%

Example I93.5: R1= cyclohexyl, R2= methyl, R3= 4-amino-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine

A mixture of I93.4 (0.264 mmol, 0.090 g), thionyl chloride (2 ml) and a catalytic amount of dimethylformamide was refluxed for 2h before distillation of solvents under reduced pressure. To the residue, a solution of NH_3 (0.5N) in dioxan (4 ml) was added and the mixture was heated in a sealed tube at 80°C for 4 days. The mixture was then evaporated to dryness and the crude was diluted in a solution of acetic acid (0.1 ml AcOH in 10 mml H_2O), and extracted with dichloromethane to remove the impurities. The aqueous phase was then basified with a solution NaOH (0.1N) and then extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired product.

Yield= 7.5%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.29-1.50 (m, 5H), 1.60-1.69 (m, 1H), 1.79-1.90 (m, 4H), 2.65-2.72 (m, 1H), 3.65 (s, 3H), 5.60-5.70 (b, 2H), 7.75 (d, 1H), 7.90 (s, 1H), 7.98 (d, 1H), 8.67 (s, 1H).

MS (m/z) / M+1= 341/343

HPLC (uv purity, λ= 214 nm): 99.99%

Example I93.6: R1= cyclohexyl, R2= methyl, R3= 2,4-Dioxo-1,2,3,4-tetrahydro-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione

To a solution of I93.3 in THF (4ml), carbonyldiimidazole (0.464 mmol, 0.080 g) was added and the reaction was heated at reflux overnight. Carbonyldiimidazole (0.464 mmol, 0.080 g) was added and the mixture was kept at reflux for 24h. Then, the solvent was distilled and the residue was purified by chromatography on silica gel, eluting with a gradient of cyclohexane containing from 15 to 30%. The chromatographied

product was solubized in ethylacetate and the organic layer was washed with water. The collected organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give the title product.

Yield= 13.3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.28-1.39 (m, 5H), 1.56-1.64 (m, 1H), 1.72-1.82 (m, 4H), 2.62-2.67 (m, 1H), 3.54 (s, 3H), 7.41-7.43 (m, 2H), 7.94 (d, 1H), 11.17 (s, 1H), 11.36 (s, 1H).

MS (m/z) / M+1 = 358/359

HPLC (uv purity, λ= 214 nm): 96.70%

Example I94: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-sulfamoyl-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

The title compound was prepared by the procedure described in example I19 (protocol C) using the appropriate intermediates and reagents. The residue was purified by chromography on silica gel, eluting with dicloromethane containing from 0 to 2% of methanol.

Yield= 59%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.63-1.69 (m, 1H), 1.77-1.87 (m, 4H), 2.59-2.67 (m, 1H), 3.60 (s, 3H), 4.06 (s, 3H), 5.02 (s, 2H), 7.20 (d, 1H), 7.40 (s, 1H), 7.90 (d, 1H).

MS (m/z) / M+1 = 384/386

HPLC (uv purity, λ= 214 nm): 99.99%

Example I95: R1= cyclohexyl, R2= methyl, R3= 4-methoxy-3-sulfamoyl-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

The title compound was prepared by procedure as described in example I18 (protocol C) using the appropriate intermediates and reagents.

In this particular case, the residue obtained after extraction and distillation was triturated with methanol and the precipitate was filtered off and purified by silica gel chromatography, eluting with a mixture of cyclohexane/ ethylacetate (1/1).

Yield= 9%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.30-1.50 (m, 5H), 1.62-1.70 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.65 (m, 1H), 3.58 (s, 3H), 4.02 (s, 3H), 5.10 (s, 2H), 7.09 (d, 1H), 7.80 (d, 1H), 8.12 (s, 1H).

MS (m/z) / M+1 = 383/384

HPLC (uv purity, λ= 214 nm): 99.38%

Example I96: R1= 3-methoxycarbonyl-phenyl, R2= methyl, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

To a solution of 7j (1.25 mmol, 0.42 g) in anhydrous dioxane (14 mL), was added methyltrifluoromethane sulfonate (1.5 mmol, 142 µl). The resultant mixture was stirred for 24h at room temperature. To this solution was added methyltrifluoromethane sulfonate (0.45 mmol, 43 µl) to ensure completion of the reaction. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by 2 sucessive flash chromatographies (eluent: dichloromethane/methanol 95/5 and cyclohexane/ethyl acetate 90/10) to give the desired compound 0.23 g (yield 53%).

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.75 (s, 3H), 3.86 (s, 3H), 7.34(d, 1H), 7.54 (t, 1H), 7.61 (s, 1H), 7.67-7.70 (m, 2H), 7.94 (d, 1H), 8.02 (d, 1H), 8.12(s, 1H).

MS (m/z) / M+1: 351/353

Example I96.1: R1= 3-benzoic-acid, R2= methyl, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A mixture of I96 (3 mg, 8.56 mmol) and potassium hydroxyde (1N in water, 12.8 mmol, 12.8mL) in tetrahydrofuran (90 ml) was stirred at room temperature overnight. The reaction mixture was heated at reflux for 1h. After cooling, the reaction mixture is concentrated, water is added (2 mL) and a solution of HCl (1N in water, 12.8 mmol, 12.8 mL) is added. The precipitate is collected by filtration and washed succesively with water and with ether before being dried under vacuum at 45°C. The compound was purified by flash chromatography (eluent: dichloromethane/methanol 99/1 +1% acetic acid) to give 2.38 g of the title product

Yield: 83%

^{1}H-NMR (400 MHz , DMSO) δ ppm : 3.8 (s, 3H), 7.31 (d, 1H), 7.51 (t, 1H), 7.61 (s, 1H), 7.65-7.69 (m, 2H), 7.93 (d, 1H), 8.01 (d, 1H), 8.11 (s, 1H), 13.06 (s, 1H).

MS (m/z) / M+1 = 337/338

HPLC (uv purity, λ= 245 nm): 99.6%

Example I97: R1= 3-methoxycarbonyl-phenyl, R2= methyl, R3= 2-pyridyl

3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

To a solution of 7k (1.76 mmol, 0.55 g) in anhydrous dioxane (14 mL) and triethylamine (1.76 mmol, 264 μL), methyltrifluoromethane sulfonate (1.76 mmol, 199 μL) was added. The resultant mixture was stirred for 24h. To this solution was added methyltrifluoromethane sulfonate (0.53 mmol, 60 μL) and triethylamine(0.53 mmol, 79.2 μL) to allow reaction to completion. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude

material was purified by filtration on silica gel (eluent: dichloromethane) to give the desired compound.

Yield: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.76 (s, 3H), 3.86 (s, 3H), 7.35 (dd, 1H), 7.48-7.54 (m, 2H), 7.64-7.68 (m, 2H), 7.96-8.00 (m, 2H), 8.58 (d, 1H).

MS (m/z) / M+1: 327/329

Example I97.1: R1 =3-benzoic-acid, R2= methyl, R3= 2-pyridyl
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A mixture of I97 (16 g,0.49 mmol) and potassium hydroxyde (1N in water, 0.58 mmol, 0.58 mL) in tetrahydrofuran (3ml) was stirred at room temperature for 48h. The reaction mixture was heated at reflux for 2h. After cooling, the reaction mixture is concentrated, water is added (5 mL), the aqueous layer was extrated with dichloromethane and neutralized with a solution of HCl (0.1N in water). The precipitate is collected by filtration and washed successively with water and with ether before being dried under vacuum at 45°C to give 0.08 g of the title product.

Yield: 54%

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.8 (s, 3H), 7.31 (d, 1H), 7.47-7.49(m, 2H), 7.64-7.66 (m, 2H), 7.96-7.98 (m, 2H), 8.58 (d, 1H)

MS (m/z) / M+1= 313/314/315

HPLC (uv purity, λ= 245 nm): 97.6%

Example I98: R1= 3-benzoic-acid, R2= methyl, R3= 4-Chloro-3-sulfamoyl-phenyl
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I98 was prepared by the procedure described in example I96.1 using the appropriate intermediates and reagents. In this particular case, the ester intermediate was basified with triehylamine. The title product was isolated by

chromatography on silica gel, eluting with ethylacetate / cyclohexane (15/85).

Yield=19% (2 steps)

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.73 (s, 3H), 3.85 (s, 3H), 7.35 (d, 1H), 7.54 (t, 1H), 7.62 (s, 1H), 7.70 -7.80 (m, 4H), 7.86 (d, 1H), 8.24 (s, 1H).

MS (m/z) / M+1 = 439/441

Then, A solution (1N) of potassium hydroxide (1.139mmol, 1.14ml) was added to a solution of the ester derivative (0.456mmol, 0.2g) in THF (5ml) and the mixture was stirred overnight. The reaction mixture was evaporated to dryness and the residue was diluted in ethanol and acidified with a solution (6.9N) of HCl in ethanol (0.165ml). The mixture was stirred at RT for 5h and the solvent was distilled under reduced pressure. The crude material was chromatographed on silica gel, eluting with a gradient of dichloromethane containing from 5 to 25% methanol. The isolated product was solubilized in THF and filtered through a pad of silica gel and the filtrate was evaporated to dryness to afford the desired product.

Yield = 37%.

^{1}H-NMR (400MHz, CDCl3) δ ppm: 3.74 (s, 3H), 7.24 (d, 1H), 7.45 (t, 1H), 7.62 (s, 1H), 7.66 (d, 1H), 7.73-7.80 (m, 3H), 7.84 (d, 1H), 8.23 (s, 1H).

MS (m/z) / M+1= 425/427

HPLC (uv purity, λ= 214 nm): 94.86%

EXAMPLE I: PROTOCOL D

Example I99: R1= cyclohexyl, R2= methyl, R3= 4-cyano-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

Compound I99 was prepared by the procedure described in exemple I15 (protocol D).

To a mixture of 4-cyanobenzoic acid (74.8 mmol, 11 g), 2-methylthiosemicarbazide 5a (74.8 mmol, 13.42 g) in anhydrous dioxane (110 mL) at 70°C, $POCl_3$ (89.65 mmol, 76.76 ml) was added and the mixture was warmed at 95°C for 4 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with dichoromethane. The organic layer was washed with water and saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate finishing with the ratio 90/10) to afford 8.5 g of the title compound.

Yield: 42%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.57-2.70 (m, 1H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.93 (dd, 2H).

Example I99.1: R1= cyclohexyl, R2= methyl, R3= 4-(1H-tetrazol-5-yl)-phenyl

Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine

To a solution of I99 (1.67 mmol, 500 mg) in toluene (2 ml), sodium azide (2.18 mmol, 142 mg), triethylamine hydrochloride (2.18 mmol; 300 mg) were added and the mixture was warmed at reflux during 24 hours. The reaction mixture was cooled at room temperature, acidified with a solution of HCl [0.1N], and then basified at pH=6-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with a saturated solution of NaCl, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel column using a gradient of dichloromethane containing from 0 to 20% methanol to afford the title compound.

Yield: 61%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.72 (m, 1H), 3.55 (s, 3H), 7.85 (dd, 2H), 8.13 (dd, 2H)
MS (m/z) / M+1= 341/342
HPLC (uv purity, λ = 214 nm)= 99.9%

Example I100: R1= cyclohexyl, R2= methyl, R3= 4-nitro-phenyl Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4] thiadiazol-2-ylidene]-amine

I100 was prepared as described in example I15 (protocol D) using the appropriate reagents. The crude material was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 10% ethylacetate.
Yield: 40%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.57-1.64 (m, 1H), 1.72-1.83 (m, 4H), 2.61-2.91 (m, 1H), 3.56 (s, 3H), 7.89 (d, 2H), 8.29 (d, 2H).
MS (m/z) / M+1 = 319/320

Example I100.1: R1= cyclohexyl, R2= methyl, R3= 4-amino-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine

Tin chloride dihydrate (93.278 mmol, 20.987 g) was added to a solution I100 (18.656 mmol, 5.940 g) in ethanol at 70°C and the mixture was refluxed for 1h30. The mixture was then filtered on Celite and the filtrate was evaporated to dryness. The crude material was basified with a saturated solution of sodium bicarbonate then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was filtred through a pad of silica gel with a mixture of dichloromethane/methanol (95/5).
Yield= 62%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.19-1.37 (m, 5H), 1.56-1.63 (m, 1H), 1.70-1.80 (b, 4H), 2.56-2.74 (m, 1H), 3.44 (s, 3H), 5.60 (s, 2H), 6.58 (d, 2H), 7.29 (d, 2H).
MS (m/z) / M+1= 289/290
HPLC (uv purity, λ= 214 nm): 97.61%

Example I100.2: R1= cyclohexyl, R2= methyl, R3= 4-(N-cyano-N'-(2-dimethylaminoethyl)carboximidamide)-phenyl
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
To a solution of diphenylcyanocarbonimidate (0.364 mmol, 0.087 mmol) in acetonitrile (1 ml) at 70°C, I100.1 (0.347 mmol, 0.1 g) was added and the reaction mixture was heated at 80°C for 15h. 1eq. of carbonimidiate was added and the mixture was kept at 80°C for an additional 5h before evaporation of volatiles. The residue was mixed with ethanol (2 ml) and N,N-dimethylethylene diamine (0.34 mmol, 0.038 mg). The mixture was stirred at room temperature for 15h and heated at reflux for 5h. On cooling to room temperature, the precipitate formed was filtered off and purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 2 to 5% methanol.
Yield= 32%
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.16-1.41 (m, 5H), 1.50-1.70 (m, 1H), 1.80-1.91 (m, 4H), 2.35 (s, 6H), 2.50-2.60 (m, 3H), 3.31-3.38 (m, 2H), 3.55 (s, 3H), 6.00-6.10 (b, 1H), 7.30 (d, 2H), 7.52 (d, 2H).
MS (m/z) / M+1 = 427/428
HPLC (uv purity, λ= 214 nm): 97.23%

Example I100.3: R1= cyclohexyl, R2= methyl, R3= 4-acetamide-phenyl
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide
To a solution of I100.1 (0.347 mmol, 0.1 g) in presence of triethylamine (0.361 mmol, 0.051 ml) in anhydrous toluene (3

ml) at 0°C, acetic anhydride (0.382 mmol, 0.036 ml) was added and the reaction mixture was stirred at room temperature for 20h and then concentrated to dryness. The residue was mixed with a saturated solution of sodium bicarbonate and then the aqueous mixture was extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography eluting with a mixture of methanol/dichloromethane (2/98).

Yield=22%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.45 (m, 5H), 1.58-1.68 (m, 1H), 1.80-1.88 (m, 4H), 2.21 (s, 3H), 2.58-2.64 (m, 1H), 3.60 (3H, s), 7.20 (s, 1H), 7.52-7.62 (m, 4H).

MS (m/z) / M+1 = 331:332

HPLC (uv purity, λ= 214 nm): 95.24%

Example I100.4: R1= cyclohexyl, R2= methyl, R3= 4-(bis-ethylesulfonyl-amino)-phenyl

[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of I100.1 (0.347 mmol, 0.1 g) in dichloromethane (5 ml) with triethylamine (0.520 mmol, 0.072 ml), chlorosulfonyl chloride (0.590 mmol, 0.057 ml) was added at 0°C and the mixture was stirred at room temperature for 4h30 before evaporation to dryness under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% methanol.

Yield= 76%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.52 (m, 11H), 1.61-1.68 (m, 1H), 1.80-1.89 (m, 4H), 2.59-2.68 (m, 1H), 3.58-3.64 (m, 7H), 7.40 (d, 2H), 7.70 (d, 2H).

MS (m/z) / M+1= 473/475

HPLC (uv purity, λ= 214 nm): 98.68%

Example I100.5: R1= cyclohexyl, R2= methyl, R3= 4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl

[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of 1,1-bis(methylthio)-2-nitroethylene (1.041 mmol, 0.172 g) in acetonitrile (1 ml), at 75°C, I100.1 (0.347 mmol, 0.1 g) was added and the reaction was heated at reflux for 7h. The reaction mixture was then evaporated to dryness and the crude material was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% of methanol to give the desired intermediate (0.09 g, yield: 64%).

A mixture of ethylenediamine (0.133 mmol, 0.017 ml) and this intermediate (0.111 mmol, 0.045 g) in ethanol (2 ml) was heated at reflux for 3h. The mixture was concentrated under reduce pressure to give a residue which was purified by silica gel chromatography eluting with dichloromethane containing 2% methanol.

Yield= 90%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.23-1.49 (m, 5H), 1.65-1.70 (m, 1H), 1.78-1.88 (m, 4H), 2.45 (s, 6H), 2.57-2.71 (m, 3H), 3.51-3.61 (m, 5H), 6.66 (s, 1H), 7.09 (d, 2H), 7.60 (d, 2H), 10.55-10.62 (b, 1H), 12.28-12.40 (b, 1H).

MS (m/z) / M+1= 446/447

HPLC (uv purity, λ= 214 nm): 99.34%

Example I100.6: R1= cyclohexyl, R2= methyl, R3= 4-(1-amino-2-nitro-vinylamino)-phenyl

(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine

The title product was prepared by the procedure described in example I100.5 using a solution of ammonia (2N) in methanol (80 eq) instead of ethylenediamine.

The desired product was isolated by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 2 to 4 % methanol.

Yield= 83%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.47 (m, 5H), 1.62-1.67 (m, 1H), 1.76-1.87 (m, 4H), 2.60-2.66 (m, 1H), 3.60 (m, 3H), 6.70 (s, 1H), 7.24 (d, 2H), 7.67 (d, 2H).

MS (m/z) / M+1 = 375/376

HPLC (uv purity, λ= 214 nm): 94.09%

Example I100.7: R1= cyclohexyl, R2= methyl, R3= 4-(*N*-cyano-*N'*-methyl-carboximidamide)-phenyl

[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of diphenylcyanocarbonimidate (0.364 mmol, 0.087 g) in acetonitrile (1 ml) at 70°C, I100-1 (0.347 mmol, 0.1 g) was added and the mixture was heated at 80°C for 15h. One equivalent of diphenylcyanocarbonimidate was added and the mixture was stirred for 5h. The mixture was concentrated under reduced pressure to give the intermediate which was used without further purification. The intermediate (0.416 mmol, 0.300 g) in a solution (2N) of methylamine in MeoH (32.890 mmol, 16.64 ml) was refluxed for 8h then allowed to stand at room temperature for 2 days. The mixture was evaporated to dryness and the residue was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 4% of methanol to give the desired product.

Yield: 29%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.45 (m, 5H), 1.62-1.67 (m, 1H), 1.76-1.87 (m, 4H), 2.57-2.67 (m, 1H), 2.90 (d, 3H), 3.60 (m, 3H), 4.90-5.01 (b, 1H), 7.17-7.28 (m, 3H), 7.69 (d, 2H).

MS (m/z) / M+1= 370/371

HPLC (uv purity, λ= 214 nm): 99.99%

Example I100.8: R1= cyclohexyl, R2= methyl, R3= 4-(N-cyano-N'-amino-carboximidamide)-phenyl

[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

The title product was prepared by the procedure described in example I100.7 using the same intermediate (0.416 mmol, 0.300 g) and a solution (2N) of ammonia in methanol (32.89 mmol, 16.64 ml). The desired product was purified by chromatography on silica gel eluting with a gradient of dichloromethane containing from 0 to 7% methanol.

Yield= 67%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.46 (m, 5H), 1.60-1.66 (m, 1H), 1.78-1.88 (m, 4H), 2.55-2.65 (m, 1H), 3.58 (m, 3H), 6.10 (s, 2H), 7.42 (d, 2H), 7.55 (d, 2H), 8.71 (s, 1H).

MS (m/z) / M+1 = 356/357

HPLC (uv purity, λ= 214 nm): 97.39%

Example I100.9: R1= cyclohexyl, R2= methyl, R3= 4-ethylsulfonylamino-phenyl

Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide

Ethylsulfonyl chloride (0.416 mmol, 0.040 ml) was added to a solution of I100.1 (0.347 mmol, 0.10 g) in dichloromethane at 0°C. The mixture was stirred for 12 h at room temperature then basified with a saturated solution of sodium bicarbonate. The organic layer was collected and concentrated under reduce pressure. The crude material was reacted with 1,1-bis(methylthio)-2-nitroethlene (2.690 mmol, 0.445 g ,10 eq) at reflux in acetonitrile (5 ml) for 24 h. The solvent was then distillated under reduced pressure and the residue was purified by silica gel chromatography eluting with dichloromethane containing a gradient from 0 to 10% methanol.

Yield= 15%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.24-1.44 (m, 8H), 1.62-1.68 (m, 1H), 1.78-1.87 (m, 4H), 2.59-2.65 (m, 1H), 3.14-3.19 (q, 2H), 3.60 (s, 3H), 6.44 (s, 2H), 7.23 (dd, 2H), 7.61 (dd, 2H).

MS (m/z) / M+1= 381/383

HPLC (uv purity, λ= 214 nm): 99.22%

Example I100.10: R1= cyclohexyl, R2= methyl, R3= 4-Ureido-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-phenyl]-urea

To a solution of I100.1 (0.348 mmol, 0.100 g) in THF (1 ml), trimethylsilyl isocyanate (0.416 mmol, 0.488 ml) was added and the mixture was stirred at room temperature for 10 h and water was added. The organic layer was extracted with ethylacetate, washed with water, brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The crude product was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 4% of methanol.

Yield= 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.24-1.39 (m, 5H), 1.53-1.57 (m, 1H), 1.69-1.80 (m, 4H), 2.57-2.65 (m, 1H), 3.47 (s, 3H), 5.92 (s, 2H), 7.50 (s, 4H), 8.79 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm): 92.50%

Example I100.11: R1= cyclohexyl, R2= methyl, R3= 4-[3-(2-dimethylamino-ethyl)-ureido]-phenyl

1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea

To a solution of I100.1 (0.347 mmol, 0.100 g) with triethylamine (1.041 mmol, 0.145 ml) in dichloromethane anhydrous (5 ml), was added a solution of phosgene (20% in toluene) (1.024 mmol, 0.487 ml) at 0°C. The mixture was stirred at 0°C for 10 min then allowed to raise to room temperature for 1h and N,N-dimethyl-ethylene diamine (0.694 mmol, 0.076 ml) was added. After 20 h of stirring at room temperature, the mixture was basified with a saturated solution of sodium bicarbonate then extracted with dichloromethane. The organic phase was washed with water, brine , dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel

eluting with a mixture dichloromethane/methanol (95/5) to afford the tittle product.

Yield= 11%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.70-1.75 (m, 1H), 1.78-1.90 (m, 4H), 2.33 (s, 6H), 2.58-2.68 (m, 3H), 3.30-3.40 (b, 2H), 3.60 (s, 3H), 5.37-5.47 (b, 1H), 7.40 (d, 2H), 7.55 (d, 2H).

MS (m/z) / M+1 = 403/404

HPLC (uv purity, λ= 214 nm): 99.99%

Example I101: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-sulfamoyl-phenyl

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

The title compound was prepared by the procedure described in example I15 (protocol D) using the appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel, eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.

Yield: 23%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.69 (m, 1H), 1.79-1.87 (m, 4H), 2.59-2.69 (m, 1H), 3.60 (m, 3H), 5.10 (s, 2H), 7.58 (d, 1H), 7.80 (s, 1H), 8.10 (d, 1H).

MS (m/z) / M+1 = 388/389

HPLC (uv purity, λ= 214 nm): 98.32%

Example I102: R1=cyclohexyl, R2= methyl, R3= 3-chloro-4-methoxycarbonyl-phenyl

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I102 was prepared by procedure as described in example I15 (protocol D) using the appropriate intermediates and reagents. The desired product was isolated by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 7% ethylacetate. (yield : 12%)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.48 (m, 5H), 1.60-1.67 (m, 1H), 1.78-1.87 (m, 4H), 2.58-2.66 (m, 1H), 3.60 (s, 3H), 4.93 (s, 3H), 7.55 (d, 1H), 7.71 (s, 1H), 7.86 (d, 1H).

Example I102.1: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-benzamide

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of I102 (0.391 mmol, 0.147 g) in a mixture of THF/ MeOH (2 ml) (1/1), Lithium hydroxyde (0.430 mmol, 0.010 g) was added and the raction mixture was allowed to stir for 15h at room temperature. Lithium hydroxyde (0.430 mmol, 0.010 g) was added and the reaction was stirred for 24 h before evaporation to dryness. The crude material was acidified with a solution of HCl (1N), stirred at room temperature for 3h and the mixture was then concentrated to dryness.

Toluene (5 ml) was added to the residue (0.273 mmol, 0.120 g) followed by an addition of thionyl chloride (0.820 mmol, 0.598 ml) and the mixture was heated at reflux overnight before distillation of volatiles under reduced pressure. The residue was poured into THF (5 ml) and cooled to 0°C then a solution of concentrated ammonia (6.833 mmol, 0.448 ml) was added. The reaction was allowed to stir at room temprature for 3 h and then the solvent was distilled. The residue was purified by chromatography on silica gel, eluting with dicloromethane containing from 0 to 1% methanol.

Yield: 63% (overall)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.48 (m, 5H), 1.62-1.69 (m, 1H), 1.79-1.88 (b, 4H), 2.58-2.67 (m, 1H), 3.60 (m, 3H), 5.86-5.93 (b, 1H), 6.38-6.48 (b, 1H), 7.57 (d, 1H), 7.70 (s, 1H), 7.87 (d, 1H).

MS (m/z) / M+1= 351/353

HPLC (uv purity, λ= 214 nm): 96.60%

Example I103: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-benzamide

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

The title compound was prepared by the procedure described in example I102.1 using the appropriate intermediates and reagents (protocol D).

Yield: 47%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.42 (m, 5H), 1.60-1.69 (m, 1H), 1.77-1.89 (b, 4H), 2.55-2.65 (m, 1H), 3.60 (m, 3H), 5.89-6.00 (b, 1H), 6.30-6.40 (b, 1H), 7.46 (d, 1H), 7.68 (d, 1H), 8.00 (s, 1H).

MS (m/z) / M+1 = 351/353

HPLC (uv purity, λ= 214 nm): 98.70%

<u>PROTOCOL E</u>: Intermediate 8

R1= cyclohexyl, R2= methyl, R3= 4-methoxycarbonyl-phenyl

1-(4-methoxycarbonyl-benzoyl)-2-methyl-4-cyclohexyl-thiosemicarbazide

To a stirred solution of 5a (2.517 mmol, 0.456 g) in pyridine (6ml), methyl-4-chloro carbonyl benzoate (2.517mmol, 0.500g) was added. The mixture was stirred 24h at RT, and then the pyridine was distilled under reduced pressure. The residue was poured into water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over MgSO4 and concentrated to dryness to afford 1.10g of product.

1H-NMR (400MHz, DMSO) δ ppm: 1.15-1.25 (m, 5H), 1.51-1.61 (m, 1H), 1.61-1.71 (m, 2H), 1.71-1.87 (m, 2H), 3.28 (s, 3H), 3.9 (s, 3H), 4.10-4.21 (m, 1H), 8.00-8.10 (m, 4H), 8.59 (d, 1H), 10.79 (s, 1H).

<u>EXAMPLE I : PROTOCOL E</u>

Example I104: R1= cyclohexyl, R2= methyl, R3= 4-methoxycarbonyl-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester

A stirred mixture of the previous intermediate 8 (2.517 mmol, 1.10 g) and methanol (50 ml) was warmed until a homogeneous solution was obtained then mercury oxide (10.068 mmol, 2.18 g) was added. After 18h at reflux, 3 more equivalents of HgO were added and the reaction was kept at reflux for an additionnal 6h then allowed to cool down to RT. The reaction was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure . The crude material was purified by chromatography on silica gel eluting with cyclohexane containing from 10 to 20% ethylacetate.

Yield= 44%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.1-1.4 (m, 5H), 1.53-1.61 (m, 1H), 1.69-1.80 (m, 1H), 3.30 (s, 3H), 3.40-3.48 (m, 1H), 3.88 (s, 3H), 3.85 (d, 2H), 7.96 (d, 2H), 8.08 (d, 2H).

MS (m/z) / M+1 =316/318

Example 104.1: R1= cyclohexyl, R2= methyl, R3= 4-benzamide 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide

The title compound was prepared by procedure described in example I37.3. The desired product was isolated by chromatography on silica gel eluting with dichloromethane containing from 1 to 2 % methanol.

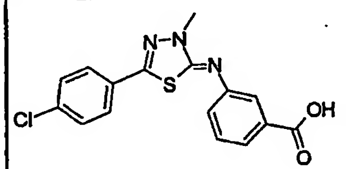
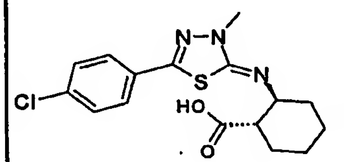
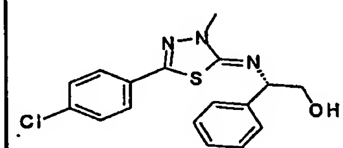
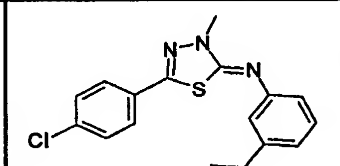
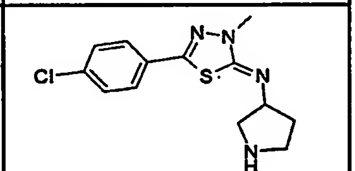
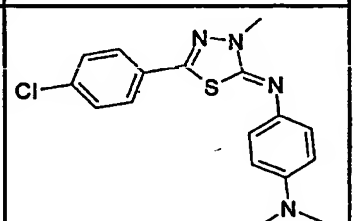
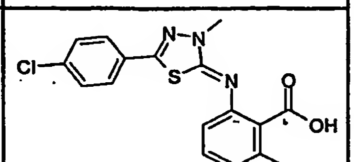
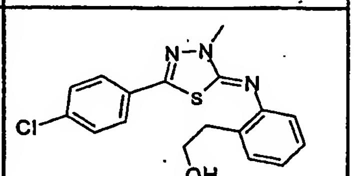
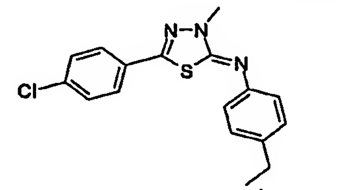
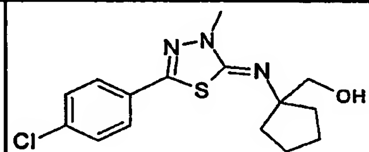
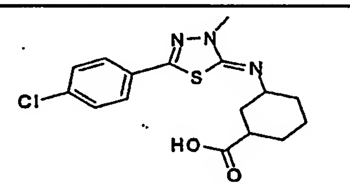
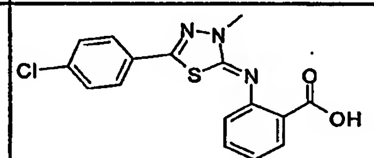
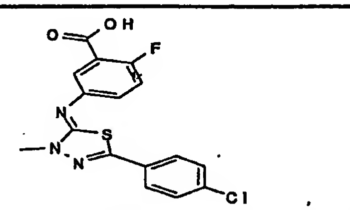
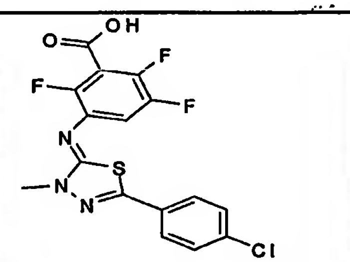
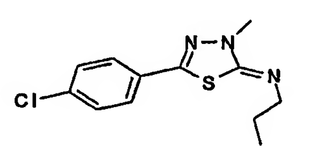
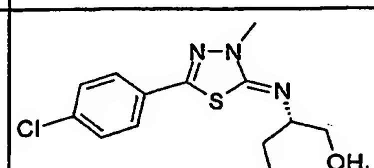
Yield= 26 % (overall)

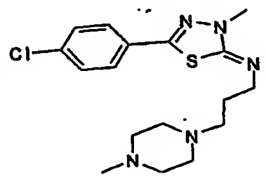
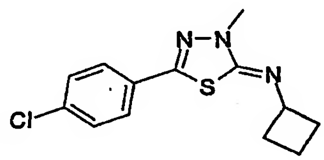
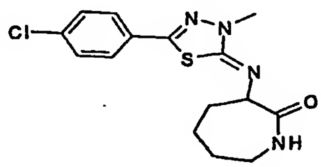
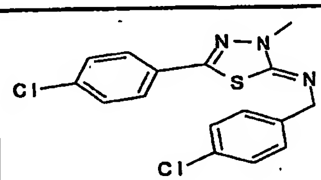
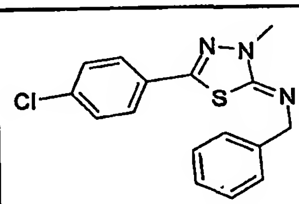
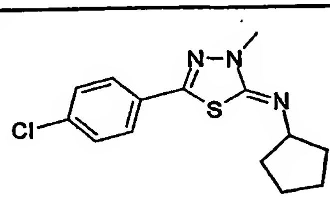
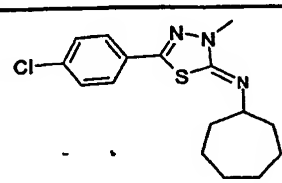
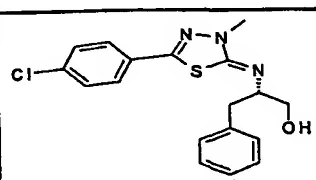
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.17-1.40 (m, 5H), 1.58-1.64 (m, 1H), 1.70-1.80 (m, 4H), 3.30 (s, 3H), 3.41-3.51 (m, 1H), 7.50-7.55 (b, 1H), 7.80 (d, 2H), 8.00 (d, 2H), 8.10-8.18 (b, 1H).

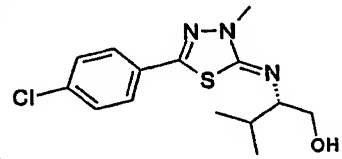
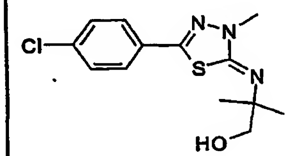
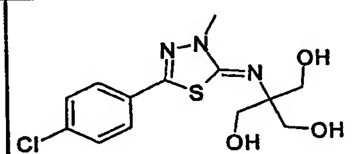
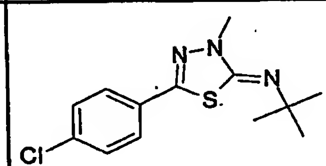
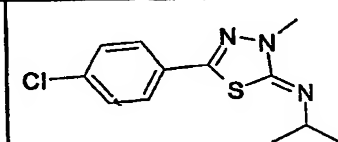
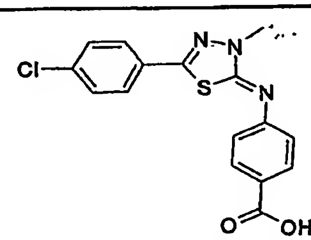
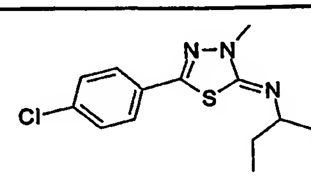
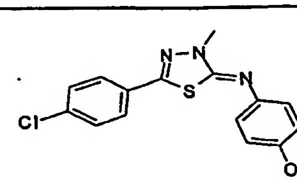
MS (m/z) / M+1 =301/302

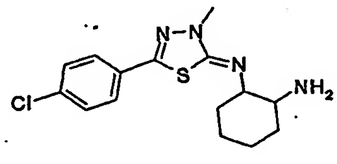
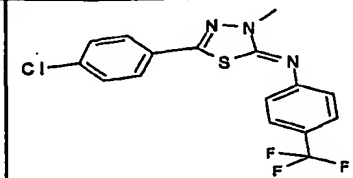
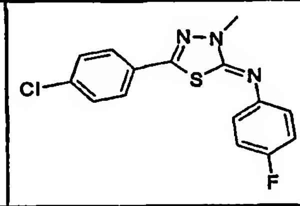
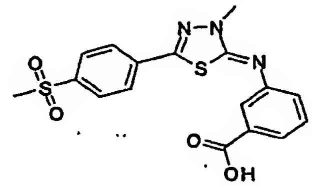
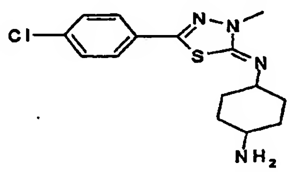
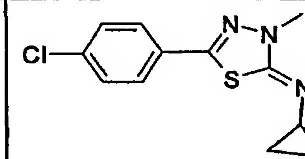
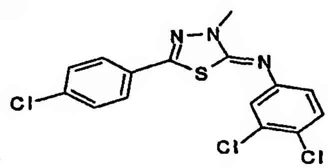
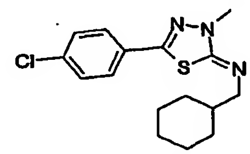
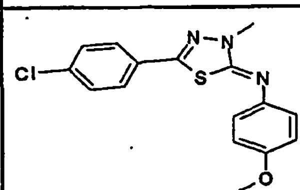
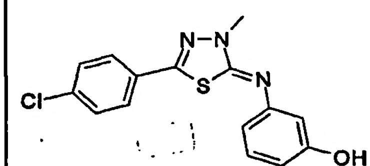
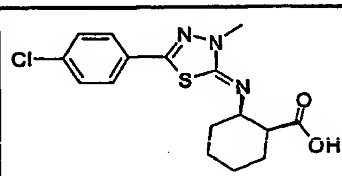
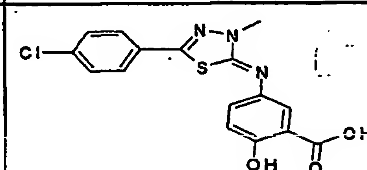
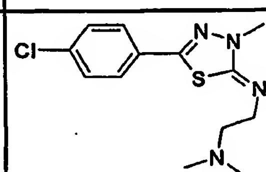
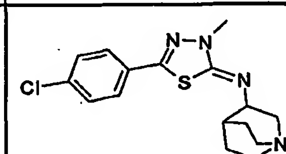
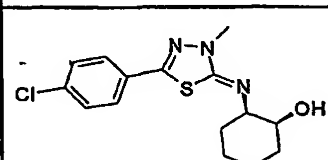
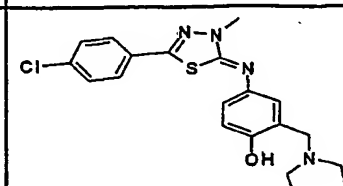
HPLC (uv purity, λ = 214 nm) = 99.9%

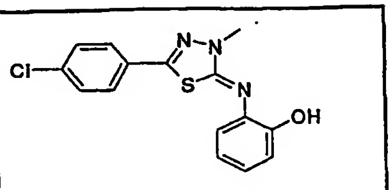
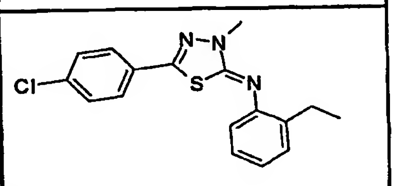
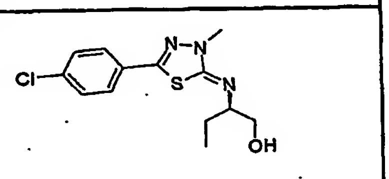
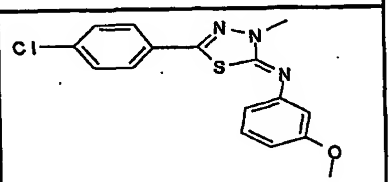
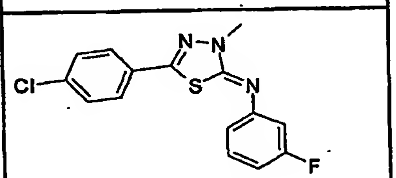
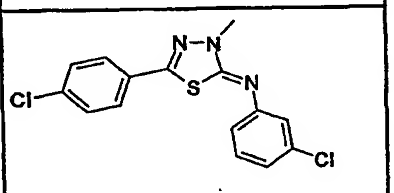
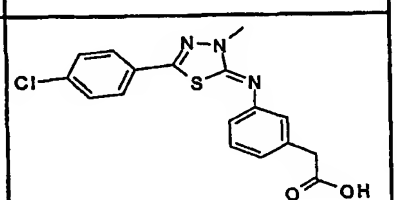
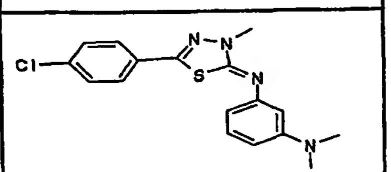
The compounds of formula (I) disclosed in the examples are summurized in the following table:

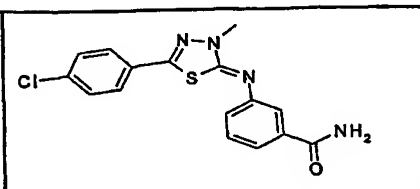
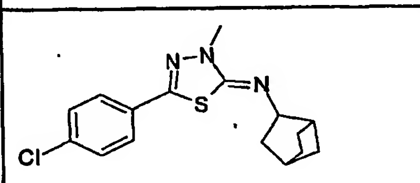
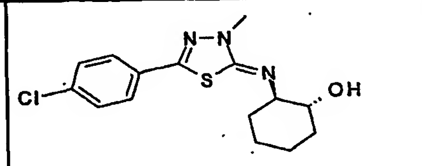
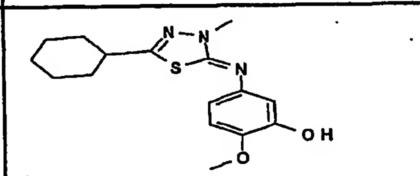
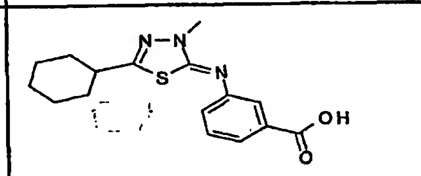
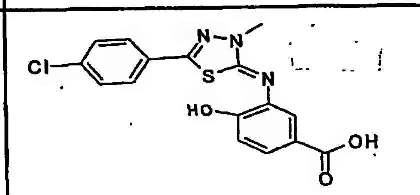
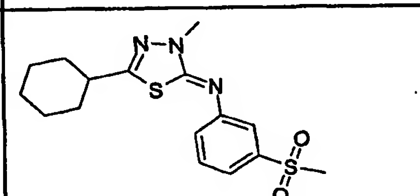
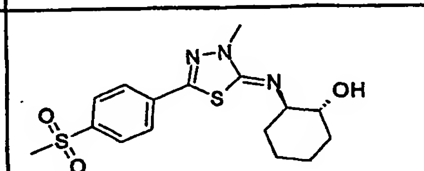
Example	Structure
I1	
I1,1	
I1,2	
I1,3	
I1,4	
I1,5	
I1,6	
I1,7	
I1,8	
I1,9	
I1,10	
I2	
I2,1	
I2,2	
I3	
I3,1	

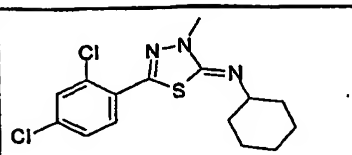
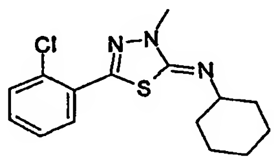
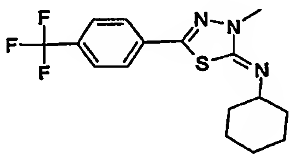
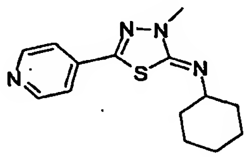
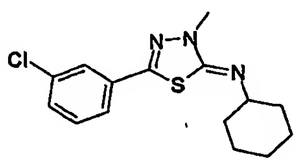
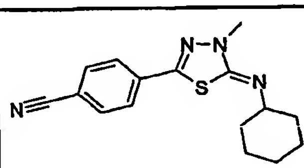
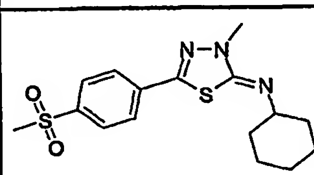
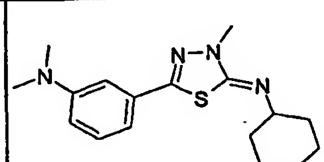
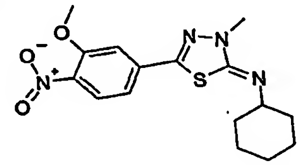
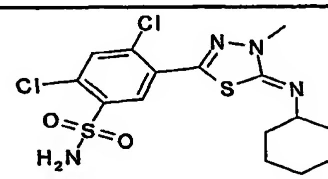
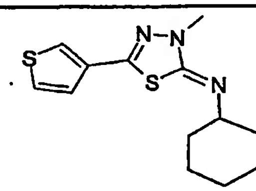
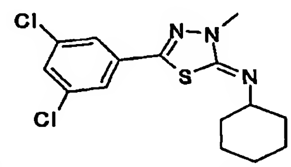
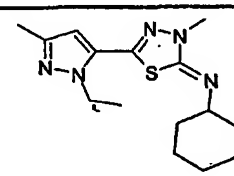
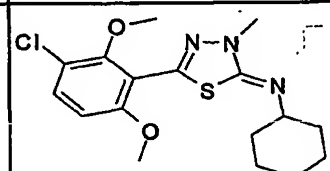
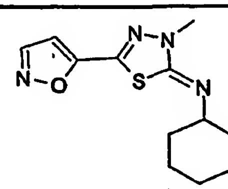
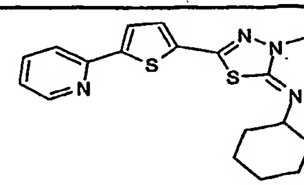
Example	Structure
I3,2	
I3,3	
I3,4	
I3,5	
I3,6	
I3,7	
I3,8	
I3,9	

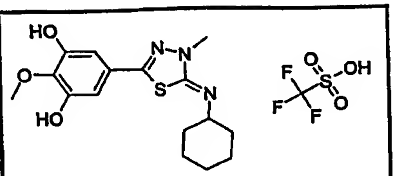
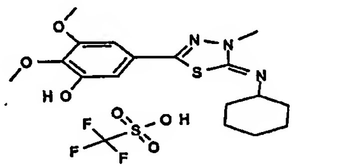
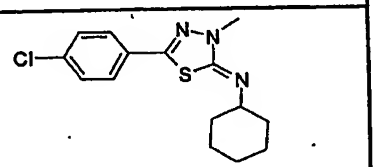
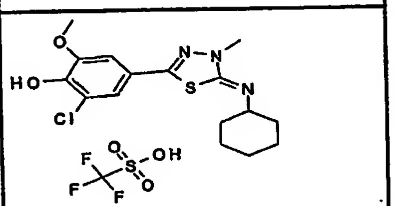
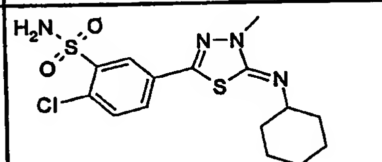
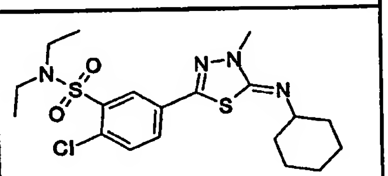
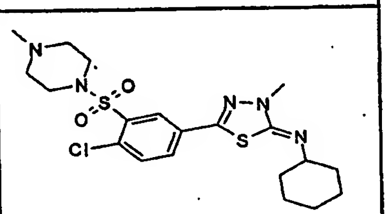
Example	Structure
I3,10	
I3,11	
I3,12	
I3,13	
I3,14	
I3,15	
I3,16	
I3,17	

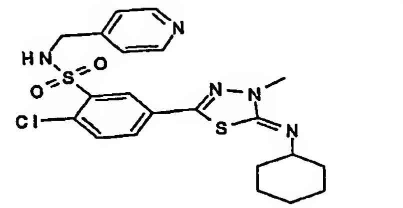
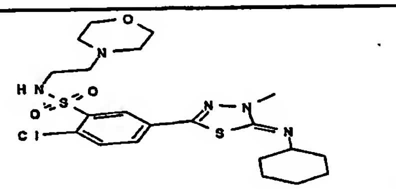
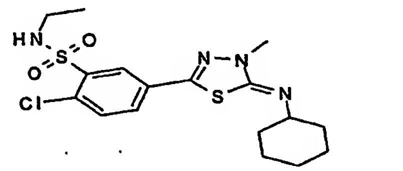
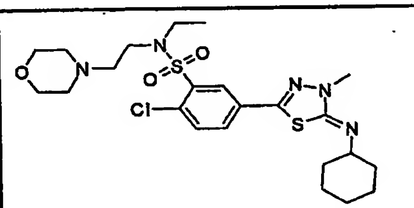
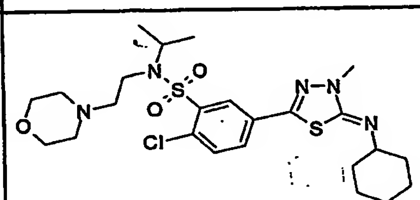
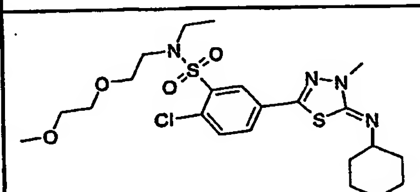
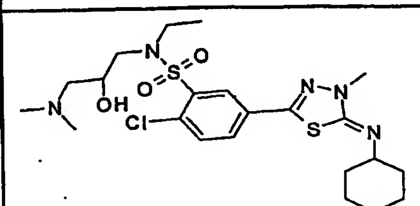
Example	Structure	Example	Structure
I3,18		I3,26	
I3,19		I4	
I3,20		I4,1	
I3,21		I4,2	
I3,22		I5	
I3,23		I6	
I3,24		I6,1	
I3,25		I6,2	

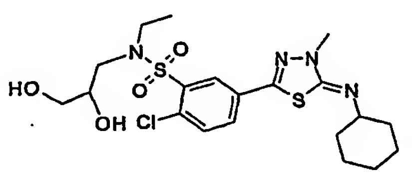
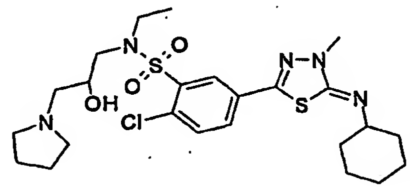
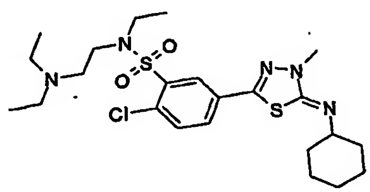
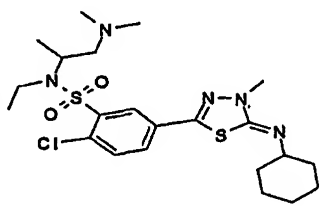
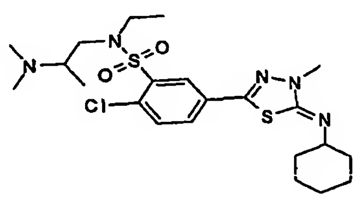
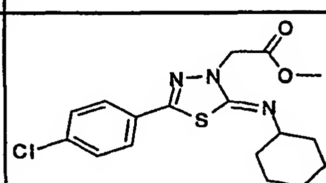
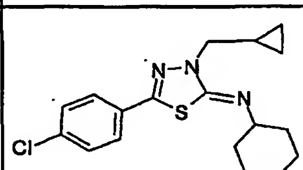
I6,3	
I6,4	
I6,5	
I6,6	
I6,7	
I6,8	
I6,9	
I6,10	

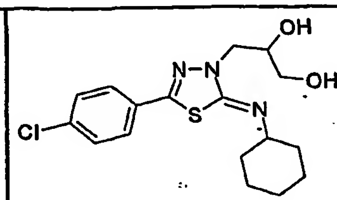
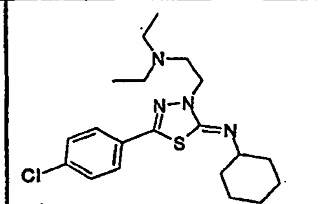
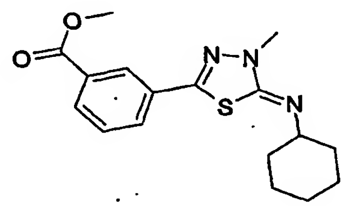
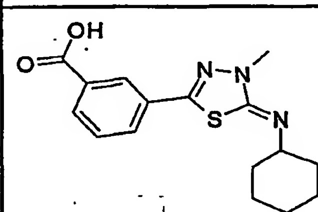
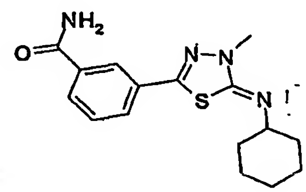
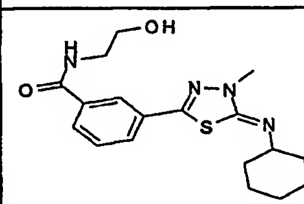
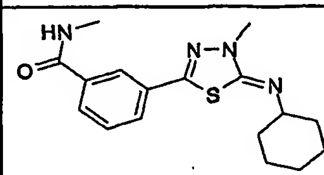
I6,11	
I7	
I8	
I8,1	
I8,2	
I8,3	
I8,4	
I9	

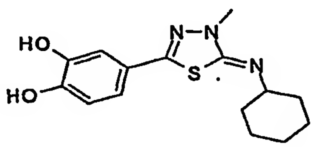
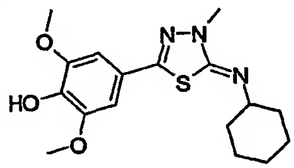
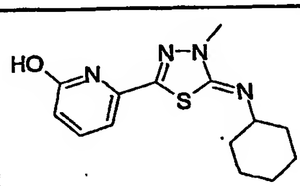
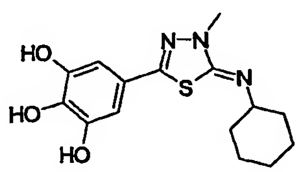
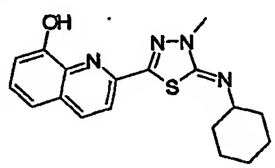
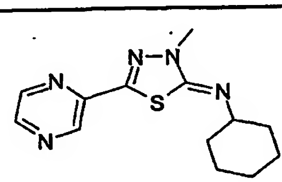
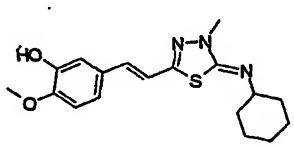
I10	
I10,1	
I11	
I12	
I13	
I14	
I15	
I15,1	
I15,2	
I16	
I17	
I17,1	
I17,2	
I18	
I18,1	
I18,2	

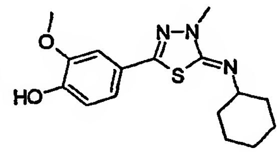
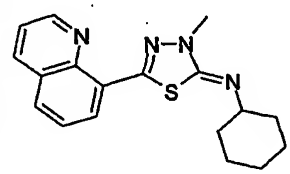
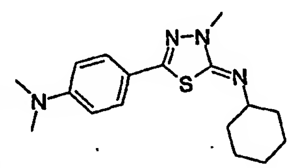
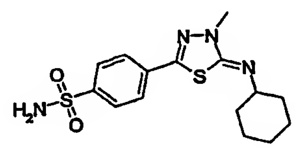
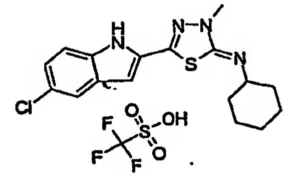
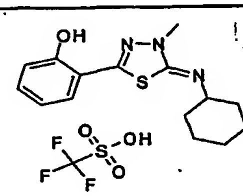
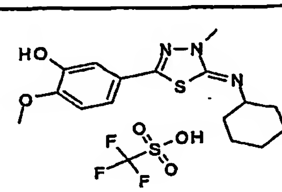
I18,3	
I18,4	
I18,5	
I18,6	
I19	
I19,1	
I19,2	

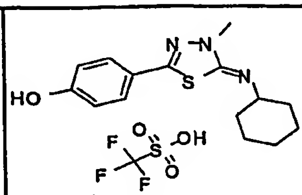
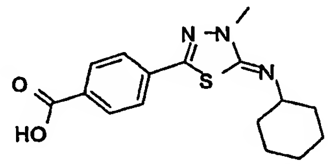
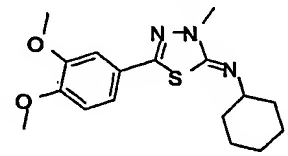
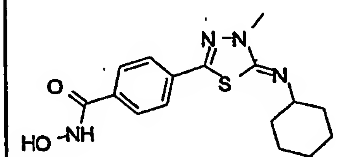
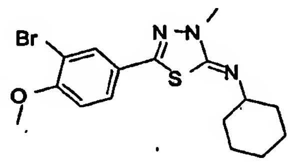
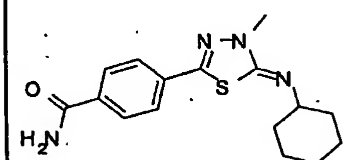
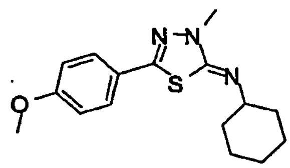
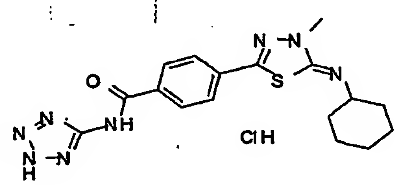
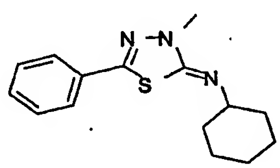
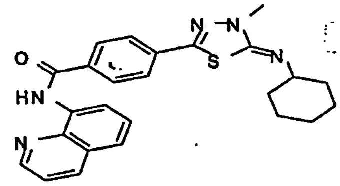
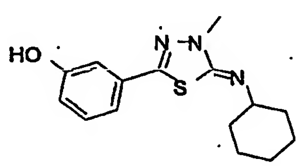
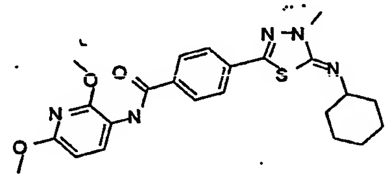
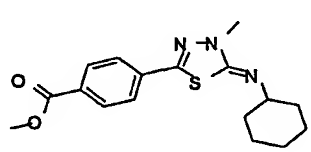
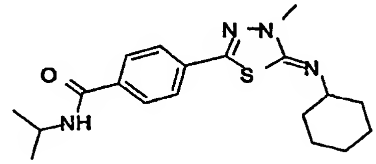
I19,3	
I19,4	
I19,5	
I19,6	
I19,7	
I19,8	
I19,9	

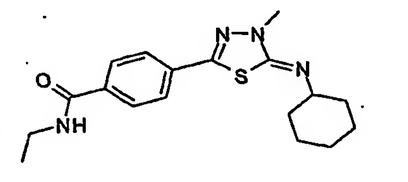
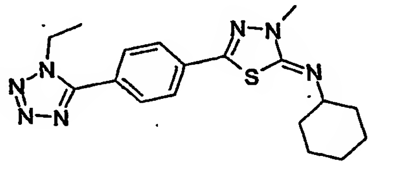
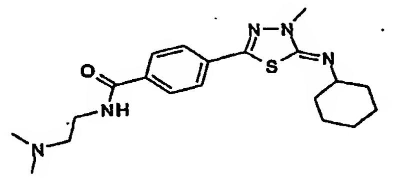
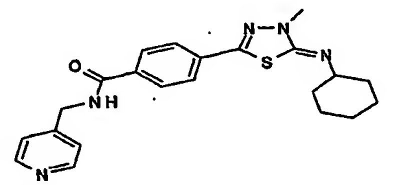
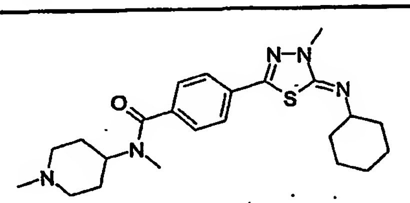
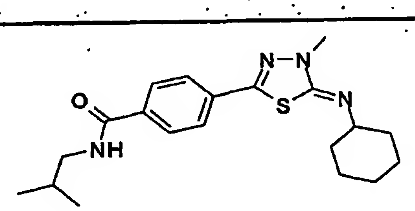
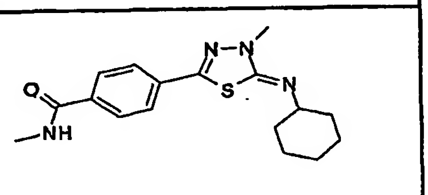
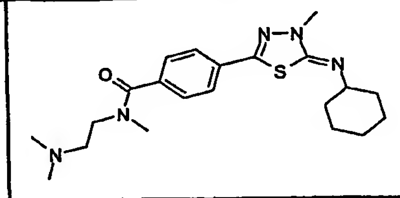
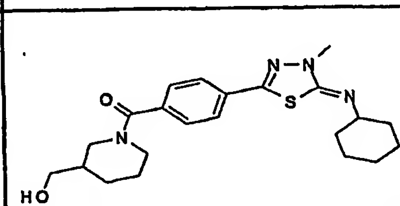
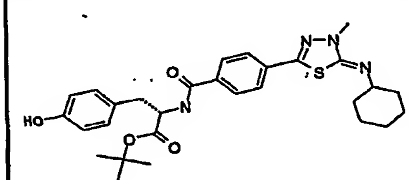
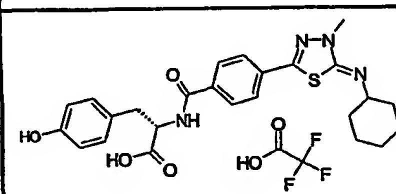
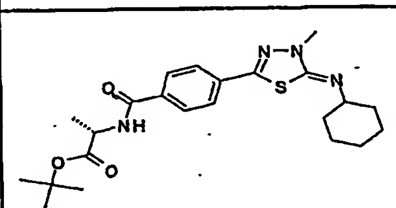
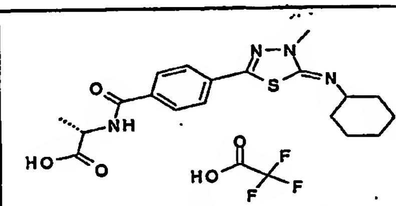
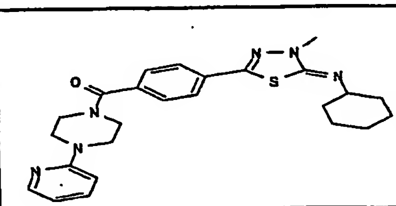
I19,10	
I19,11	
I19,12	
I19,13	
I19,14	
I20	
I20,1	

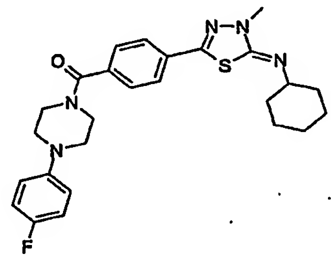
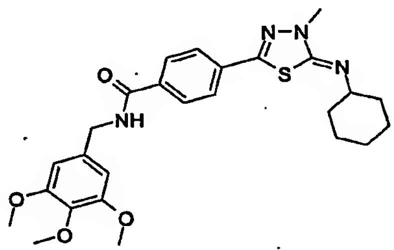
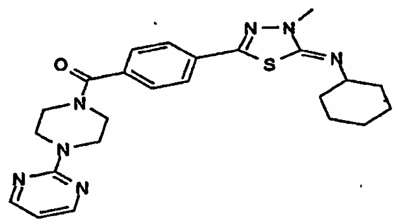
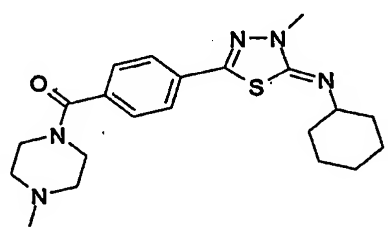
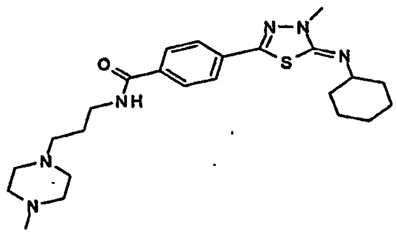
I20.2	
I20.3	
I21	
I21,1	
I21,2	
I21,3	
I21,4	

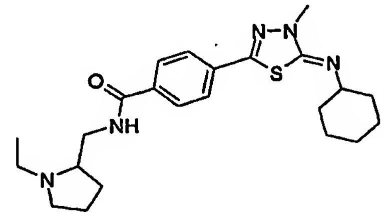
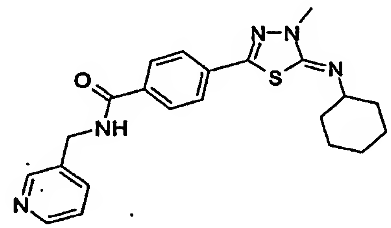
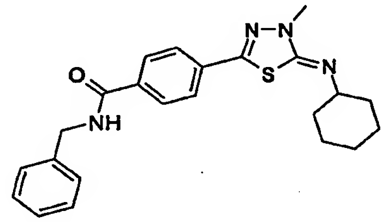
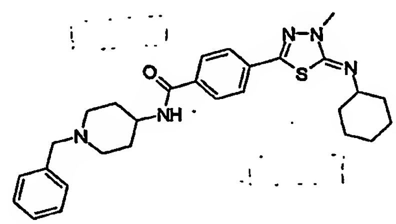
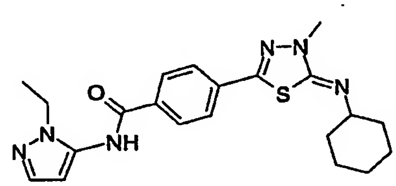
I22	
I23	
I23,1	
I23,2	
I24	
I25	
I26	

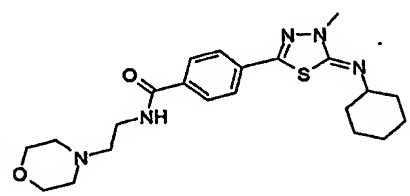
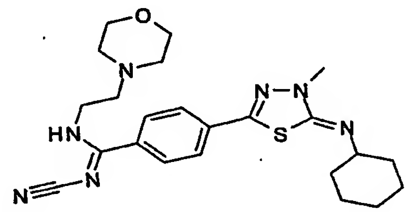
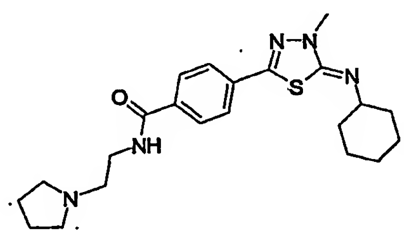
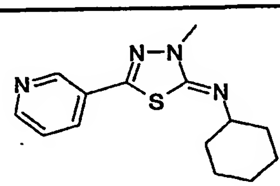
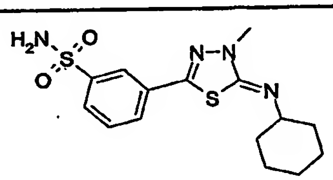
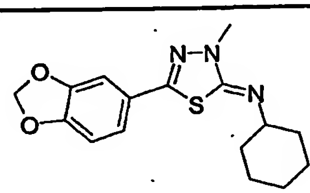
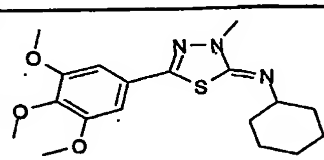
I27	
I28	
I29	
I30	
I31	
I31,1	
I32	

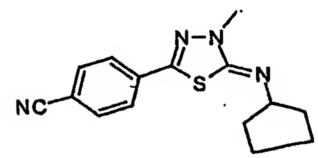
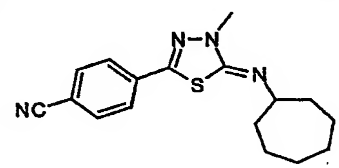
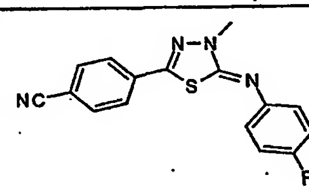
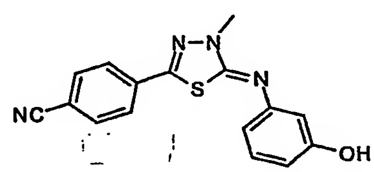
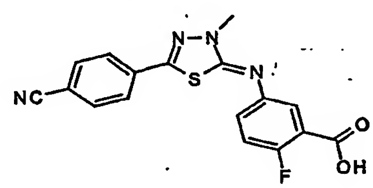
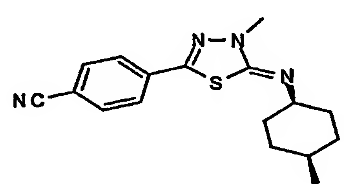
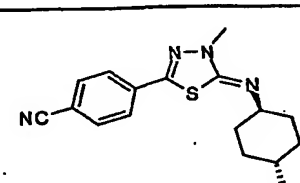
I33		I37,1	
I34		I37,2	
I35		I37,3	
I35,1		I37,4	
I35,2		I37,5	
I36		I37,6	
I37		I37,7	

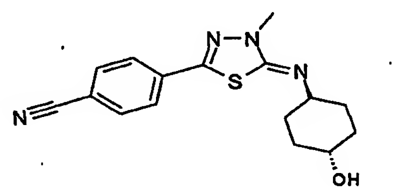
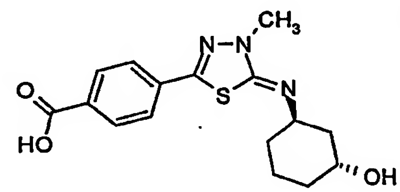
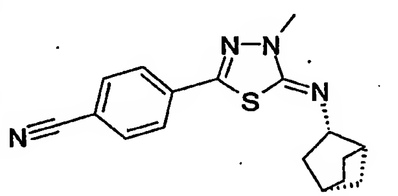
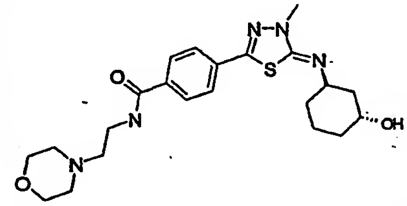
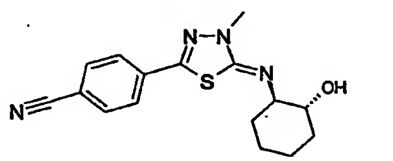
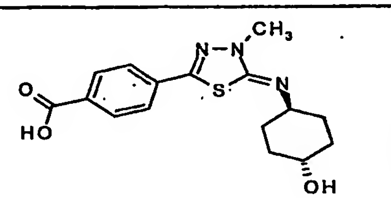
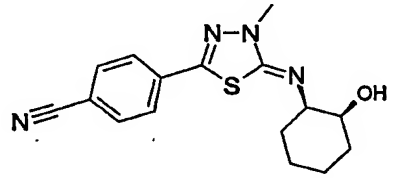
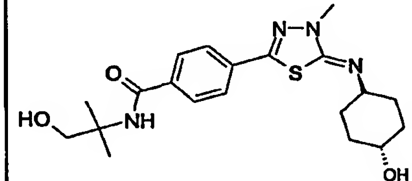
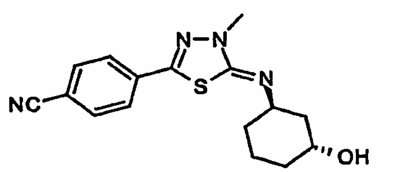
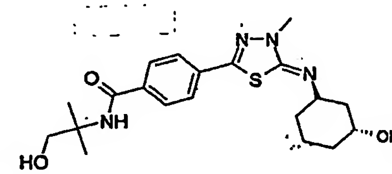
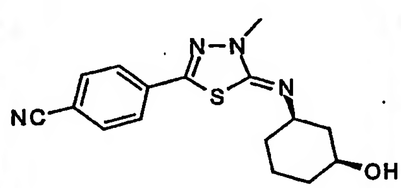
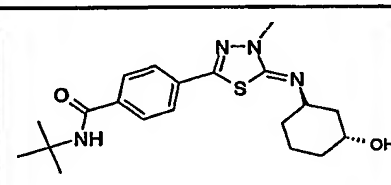
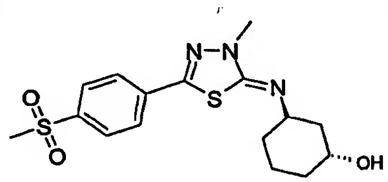
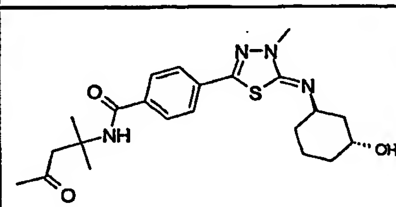
I37,8	
I37.8-1	
I37,9	
I37,10	
I37,11	
I37,12	
I37,13	
I37,13-1	
I37,14	
I37,15	
I37,15-a	
I37,16	
I37,16-a	
I37,17	

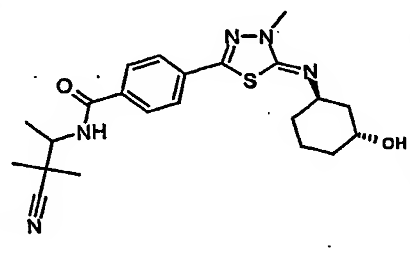
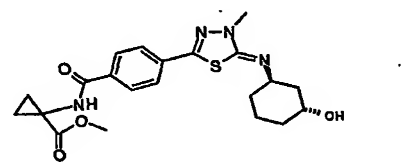
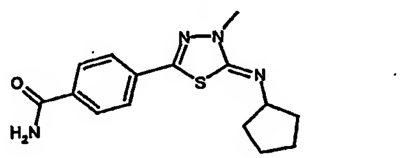
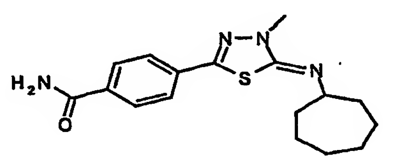
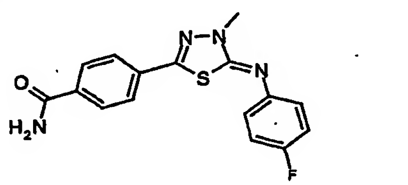
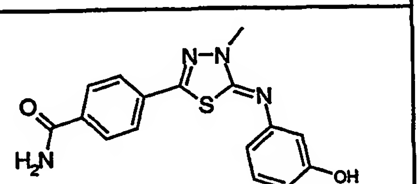
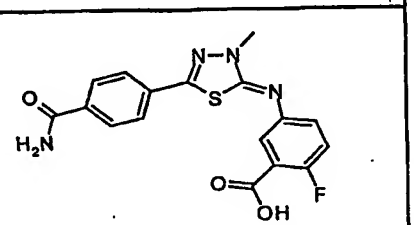
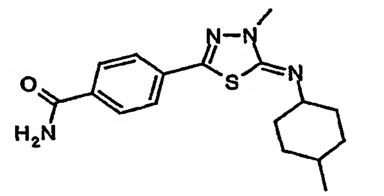
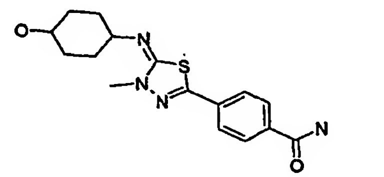
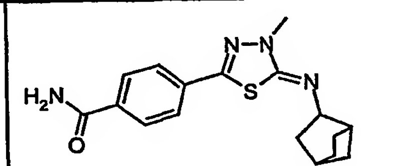
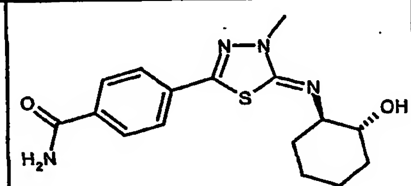
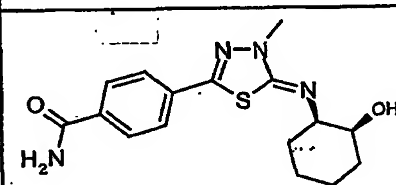
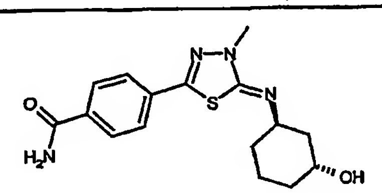
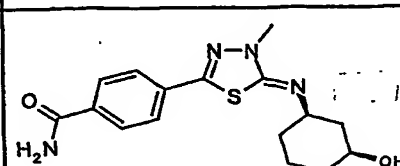
I37,18	
I37,19	
I37,20	
I37,21	
I37,22	

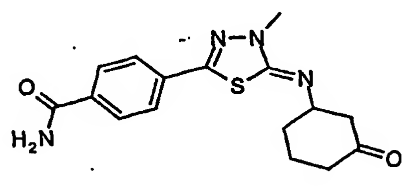
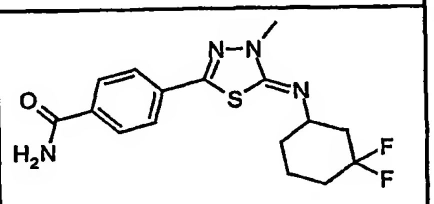
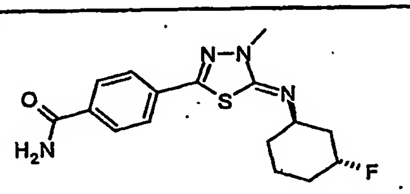
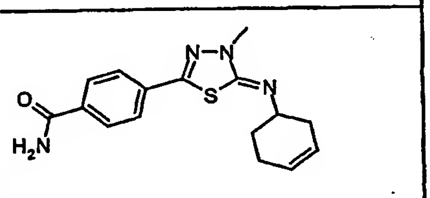
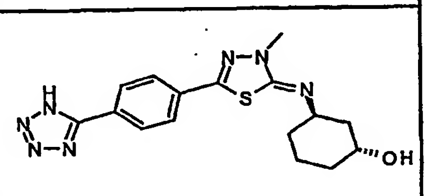
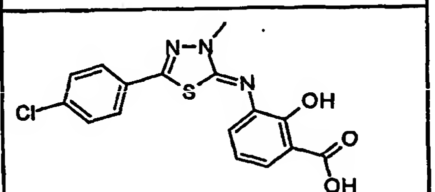
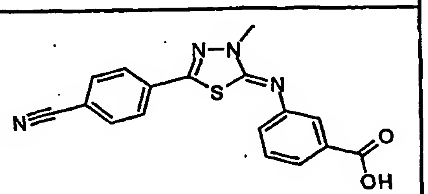
I37,23	
I37,24	
I37,25	
I37,26	
I37,27	

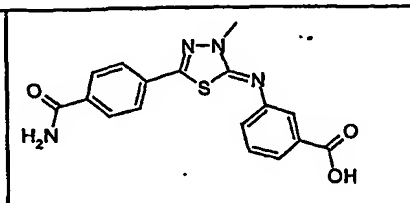
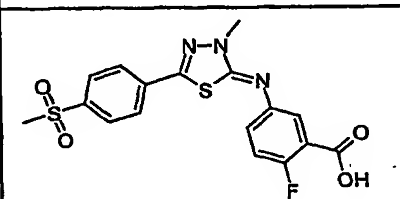
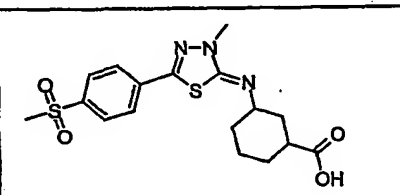
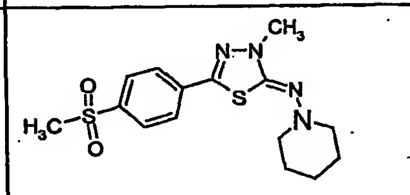
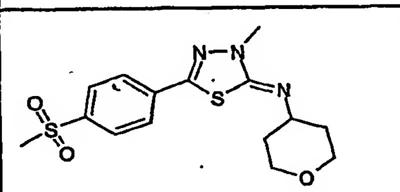
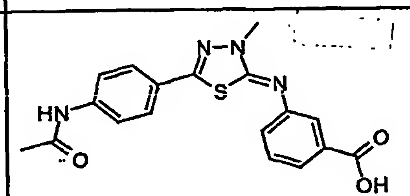
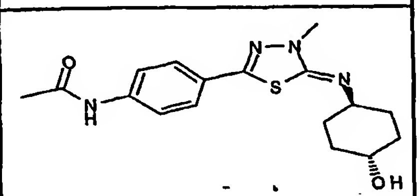
I37,28	
I37,28-1	
I37,29	
I38	
I39	
I40	
I41	

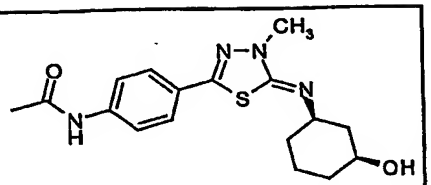
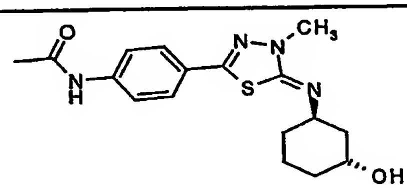
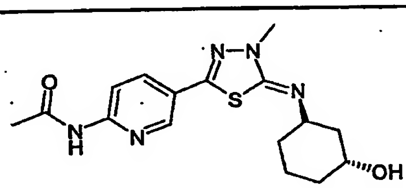
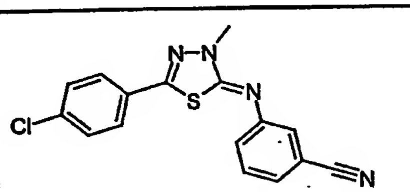
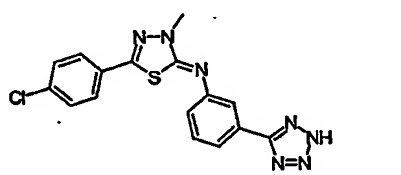
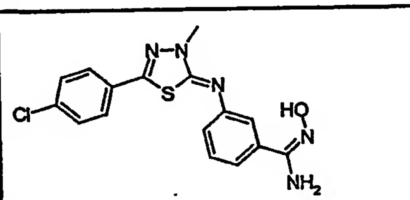
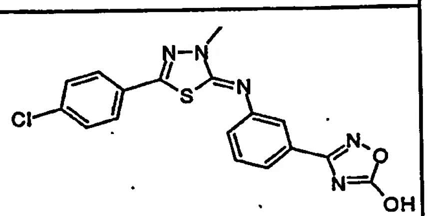
I42	
I43	
I44	
I45	
I46	
I47-a	
I47-b	

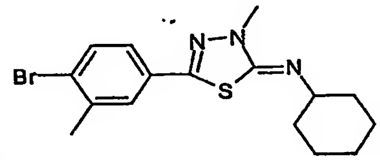
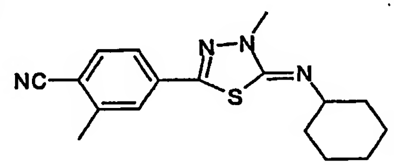
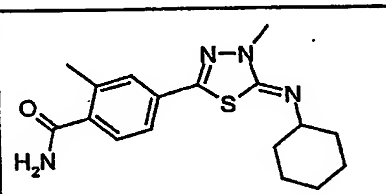
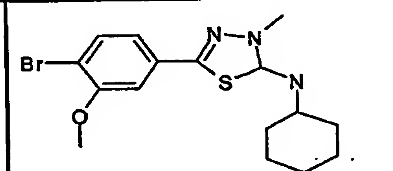
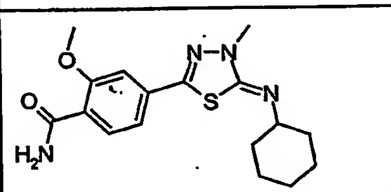
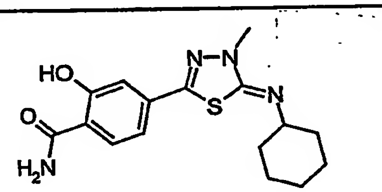
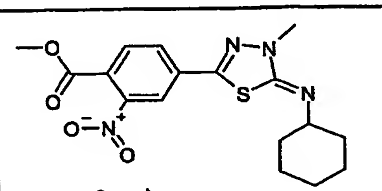
I48		I54	
I49		I55	
I50		I56	
I51		I57	
I52-a		I58	
I52-b		I59	
I53		I60	

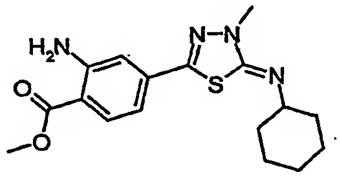
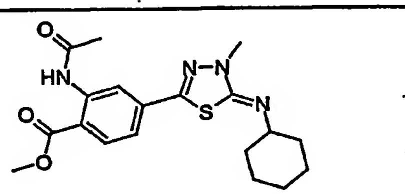
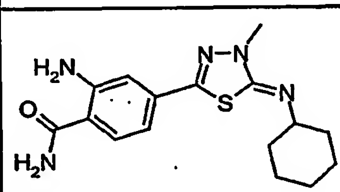
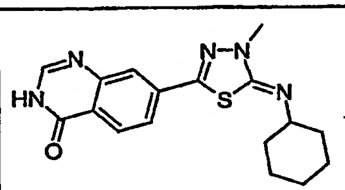
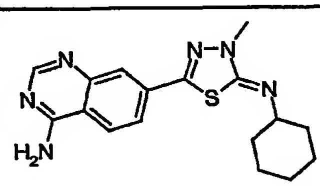
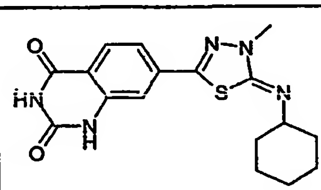
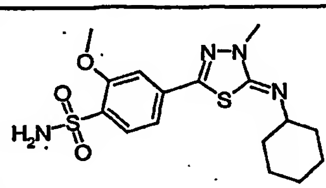
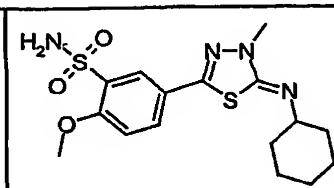
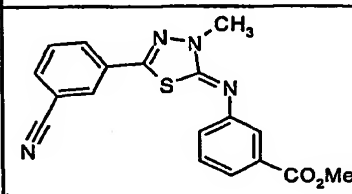
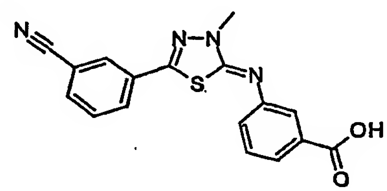
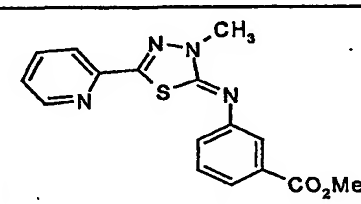
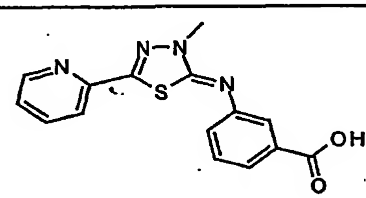
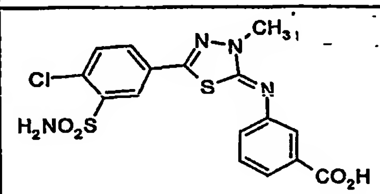
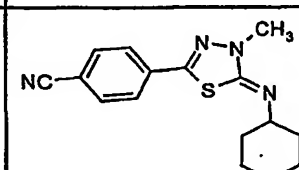
I61	
I62	
I63	
I64	
I65	
I66	
I67	
I68	
I69	
I70	
I71	
I72	
I73	
I74	

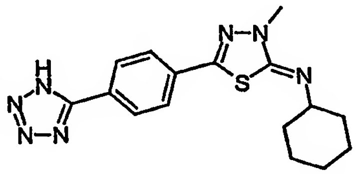
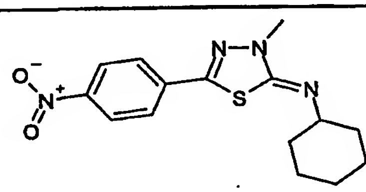
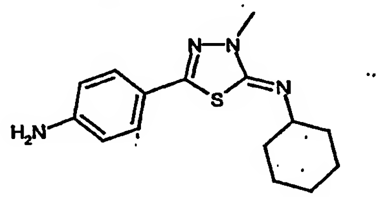
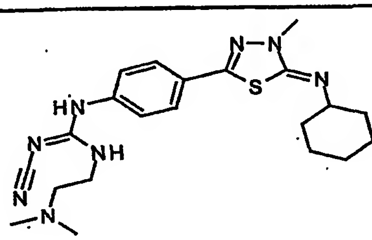
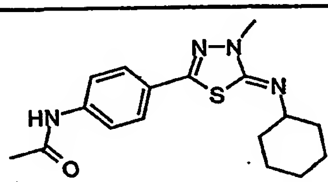
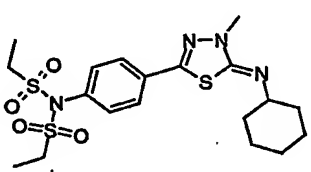
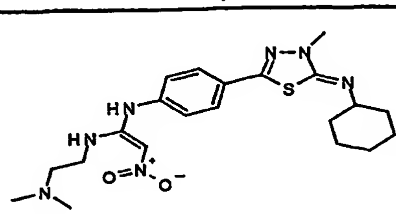
I74,1	
I75	
I76	
I77	
I78	
I79	
I80	

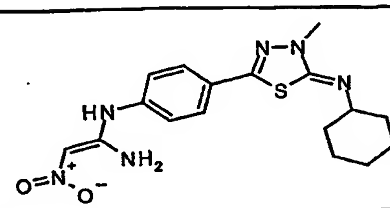
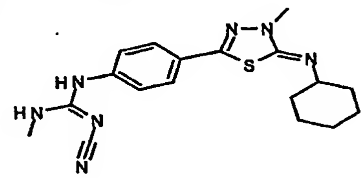
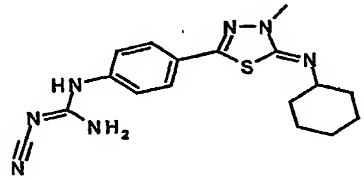
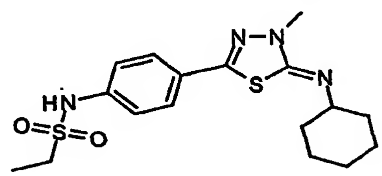
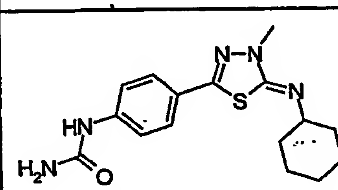
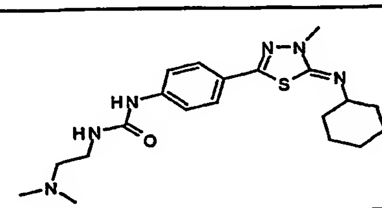
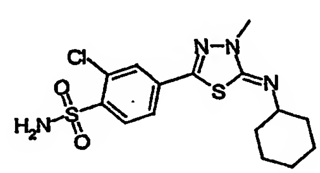
I80,1	
I81	
I82	
I83	
I84	
I85	
I86	

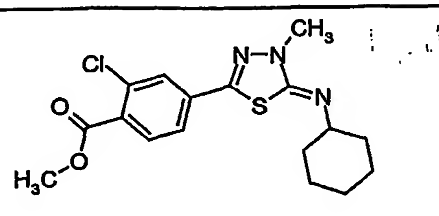
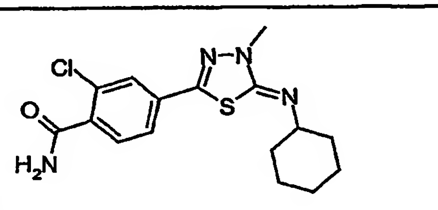
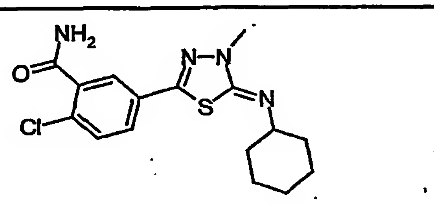
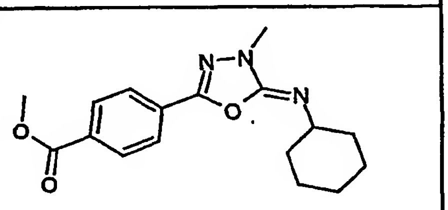
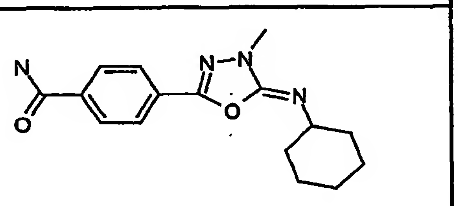
I87	
I88	
I89	
I90	
I90,1	
I90,2	
I90,3	

I91	
I91,1	
I91,2	
I92	
I92,1	
I92,2	
I93	

I93,1	
I93,2	
I93,3	
I93,4	
I93,5	
I93,6	
I94	
I95	
I96	
I96,1	
I97	
I97,1	
I98	
I99	

I99,1	
I100	
I100,1	
I100,2	
I100,3	
I100,4	
I100,5	

I100,6	
I100,7	
I100,8	
I100,9	
I100,10	
I100,11	
I101	

I102	
I102,1	
I103	
I104	
I104,1	

Biological results

In vitro inhibition of the phosphodiesterase 7 and of other phosphodiesterases

The capacity of the compounds of the invention to inhibit cyclic nucleotide phosphodiesterases was evaluated by measuring their IC_{50} (concentration necessary to inhibit the enzymatic activity by 50 %).

PDE3A3, PDE4D3, PDE7A1 were cloned and expressed in insect cells Sf21 using the baculovirus expression system. The source of PDE1C3 and of PDE5C3 were human cell lines

(respectively TPH1 human monocytes and MCF7 human caucasian breast adenocarcinoma). The various types of phosphodiesterases were obtained partially purified on an anion exchange column (Mono Q) according to a method adapted from Lavan B.E.,Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

Measurement of the enzymatic activity for the various types of PDE was then made according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92,ed. G. Brooker et al. Raven Press, NY.

The substrate used was cGMP for PDE1 and PDE5 and cAMP for PDE 3, PDE 4 and PDE 7. The substrate concentration was 0.2µM for PDE 1, PDE 3 and PDE 5, 0,25µM for PDE 4 and 50nM for PDE 7.

The enzymatic reaction was stopped after 1 hour for PDE 1, PDE 3 and PDE 5 and 10 minutes for PDE 4 and PDE 7.

In order to determine their IC_{50}, compounds of the invention were assayed at 8 concentrations ranging from 0.03nM to 100µM for PDE 4 and PDE 7 and at 6 concentration ranging from 0,1µM to 30µM for PDE 1, 3 and 5.

The IC_{50} (µM) were determined for some of the compounds of the invention, and the results are summarised in the following table:

Compounds	IC_{50} (PDE7)	Compounds	IC_{50} (PDE7)
I1	0,15	I27	0,46
I2,1	0,13	I28	0,23
I3,25	1,20	I29	0,30
I4	0,15	I30	0,14
I7	1,05	I31	0,23
I8	0,45	I32	0,23
I9	0,28	I33	0,24
I10,1	1,30	I34	0,63
I11	0,98	I35	0,58
I12	0,29	I36	0,29
I13	0,70	I37	0,23

Compounds	IC_{50} (PDE7)	Compounds	IC_{50} (PDE7)
I14	0,27	I37,1	0,55
I15	0,14	I37,2	1,2
I17,1	1,30	I37,3	0,062
I18,2	0,32	I37,4	0,15
I18,3	0,061	I37,5	0,093
I18,4	0,092	I37,6	0,097
I18,5	1,20	I37,7	0,086
I19	0,07	I37,8	0,064
I21	0,15	I37,9	0,075
I21,1	0,87	I37,10	0,044
I22	1	I37,11	0,072
I23	0,85	I38	0,34
I24	0,36	I39	0,2
I25	0,47	I40	0,45
I26	0,4	I41	1,3

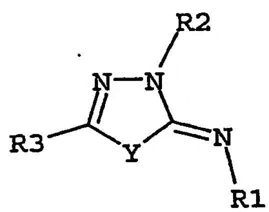
These results show that the compounds of the invention inhibit PDE7 at very low concentrations, with some IC_{50} values lower than 100nM. The results of the assays with other PDE (1, 3, 4 and 5) show IC50 values often superior to 10μM.
It demonstrates that compounds of the invention are strong and selective PDE7 inhibitors.

References

- M. Akbar Ali, S.E. Livingston, and D.J. Philipps, Inorganica Chimica Acta , 6, 11 (1972)
- P. Molina, A. Tarraga, A. Espinosa ; Synthesis, 690 (1988)
- P. Molina, A. Tarraga, A. Espinosa ; Heterocycles, vol.29, N°12 (1989)
- R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; J. Heterocyclic Chem., 33, 863 (1996)
- patent: Gulf oil corporation, WO 77 12352
- patent: Bayer AG, DE 44 18 066 A1.
- patent: Gulf oil corporation, WO 80 1507

CLAIMS

1. A compound having the following formula (I),



(I)

in which

- Y is O or S;
- R1 is:
  C_4-C_{10} alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl,
  or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, $X_5\text{-}N(R_{19})\text{-}R_{18}$ in which X_5 is a single. bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21},or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or $X_5\text{-}N(R_{19})\text{-}R_{18}$ in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,
- when X_2 is a single bond and both R1 and R'3 are phenyl, each of R1 and R'3 bear at least one substituent other than H,
- when X_2 is a single bond and R'3 is phenyl, R'3 is not substituted by an ester or a carboxylic acid in the ortho position,
- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,

1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-

ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

3. A compound of formula (I) as defined in claim 1 or 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably

CF_3, lower alkyl, carboxylic acid bioisostere,
2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,
wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,
- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:
- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$,

$C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:

cycloalkyl, preferably cyclohexane,

cycloalkenyl,

aryl, preferably phenyl,

or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.

  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,

aryl, preferably phenyl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which

R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3,
  2) COOH, OH,
  3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17},

identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) C(=O)$NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, C(=O)R_5, C(=O)NR_5R_6, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4] thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,
2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,

[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,

(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,
(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,

{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,

4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,
[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,
3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,
3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,
3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,
[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,
[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(N-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

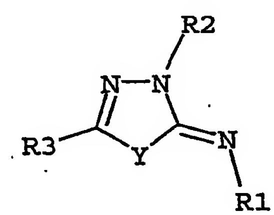
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-

ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,.
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



(I)

wherein:
- Y is O or S;
- R1 is:
  C_1-C_{10} alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl,
  or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:
  - X_1 is:
    a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,
  - R_4 is:
    1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower

alkyl, carboxylic acid bioisostere,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

2) OR_5, $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:

cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

- R_{17} is:

1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :

- H,

- lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
- X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

each optionally substituted with one or several groups which are the same or different and which are selected from:

- halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}; C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21},or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16,

comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases,

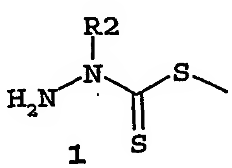
autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

25. Use according to claim 23, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

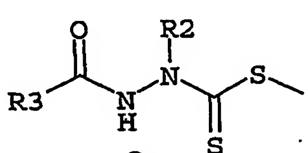
27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



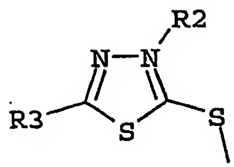
1

(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



2

(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



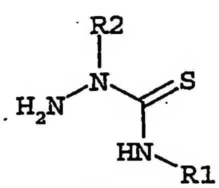
3

(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

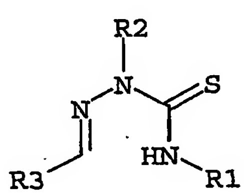
28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5



5

(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



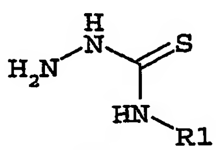
6

(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

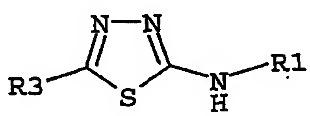
29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7



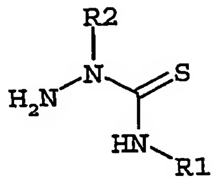
7

(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



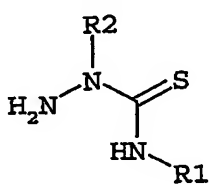
5

to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

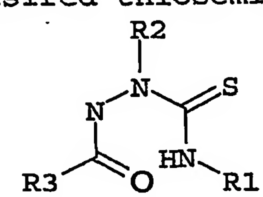
31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



5

(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



8

(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11330

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D285/135 C07D271/113 C07D417/04 C07D417/10 C07D417/12 C07D417/14 C07D453/02 A61K31/433 A61K31/55 A61K31/439 A61K31/4245 A61K31/4439 A61K31/4709 A61K31/497 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 120, no. 25, 20 June 1994 (1994-06-20) Columbus, Ohio, US; abstract no. 323458w, EL-FEKY S A ET AL: "Synthesis and biological activity of novel quinazolinones derived from 2-hydrazino-3-phenyl-4(3H)-quinazolinones" page 907; XP002162034 abstract -& DATABASE CAPLUS 'Online! Chemical Abstracts Services; Database accession no. 1994:323458 XP002162039 * RN 155389-95-0 and 155389-96-1 * & ZHONGHUA YAOXUE ZAZHI, vol. 45, no. 4, 1993, pages 303-308, ---	16-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2001	21/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE "DR. THEODOR NEUBAUER", ERFURT/MÜHLHAUSEN) 2 December 1987 (1987-12-02) the whole document	1-11,13, 31
X	HUISGEN R ET AL: "1.3-Dipolare Cycloadditionen. VI. Anlagerung der Nitrilimine an azomethine und Isocyanate" CHEMISCHE BERICHTE, vol. 97, no. 4, 3 April 1964 (1964-04-03), pages 1085-1095, XP002185163 the whole document, particularly page 1087, compound XXVI	1-11,13, 31

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L'ABBÉ G ET AL: "Synthesis and decomposition of functionalized diaziridinimines" JOURNAL OF ORGANIC CHEMISTRY, vol. 46, no. 22, 23 October 1981 (1981-10-23), pages 4478-4481, XP002185164 the whole document, particularly page 4479, compound 15b ---	1-11,13, 31
X	CHEMICAL ABSTRACTS, vol. 73, no. 11, 14 September 1970 (1970-09-14) Columbus, Ohio, US; abstract no. 56035q, GEHLEN H ET AL: "2-Amino-1,3,4-oxadiazoles. XXXV. Synthesis and reaction of 1,3,4-oxadiazolo'3,2-a!pyrimidinones" page 322; XP002185165 abstract & ARCH. PHARM. (WEINHEIM), vol. 303, no. 6, 1970, pages 501-510, ---	1-11,13, 31
X	AWASTHI A K AND AL: "A new route to 2,3,5-trisubstituted 2,3-dihydro-1,3,4-oxadiazoles via stabilized sulfuranes" SYNTHESIS, no. 7, July 1984 (1984-07), pages 590-591, XP002185166 the whole document ---	1-11,13, 31
A	WO 99 42089 A (ROCHE DIAGNOSTICS GMBH) 26 August 1999 (1999-08-26) the whole document ---	1,20-25
A	DE 37 17 232 A (VEB DEUTSCHES HYDRIERWERK RODLEBEN) 8 December 1988 (1988-12-08) the whole document -----	1,20-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/11330

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DD 251979 A	02-12-1987	DD 251979 A1	02-12-1987
WO 9942089 A	26-08-1999	AU 2926099 A	06-09-1999
		WO 9942089 A2	26-08-1999
		EP 1054669 A2	29-11-2000
DE 3717232 A	08-12-1988	DD 247003 A1	24-06-1987
		DE 3717232 A1	08-12-1988
		JP 1031788 A	02-02-1989